THE EFFECTS OF CHLORPROMAZINE UPON SOME INNATE BEHAVIORS OF MICE

by

Harold H. Wolf

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by

Harold H. Wolf

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Reader, Supervisory Committee

Head, Major Department

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I. GENERAL INTRODUCTION

A. Orientation

The study of the effects of drugs upon behavior is not a novel science. In the past there have been numerous reports in the experimental literature of the behavioral effects of alcohol, opiates, bromides, barbiturates, and other agents. However, the number of these reports appears insignificant when compared to those published since the advent of the ataractic era. This era, now approaching its tenth year, was initiated by Delay and his co-workers (1952) when they noted that chlorpromazine had an ameliorating effect in confused and agitated patients. Following this fortunate discovery, there occurred the introduction of a host of agents, all designed to provide relief from emotional discomfort. Concomitant with these developments in the drug therapy of nervous and mental diseases, there has occurred renewed interest in laboratory effects of such drugs. This interest has led to a multi-dimensional investigation of basic pharmaco-behavioral relationships, from which has arisen a new discipline known as psychopharmacology.

Psychopharmacology is a science that is concerned with the actions of drugs which influence the mind by affecting its morphologic substratum, the brain (Himwich, 1958). This new discipline can be delineated from the older science of neuropharmacology in that psychopharmacology is concerned with the effects of drugs on the behavior of an animal, whereas neuropharmacology is concerned with the over-all effects of drugs on nervous tissue. Since both neuropharmacologists and psychopharmacologists are likely to be interested in the same types of drugs, there is considerable overlap where the

two sciences meet.

Inherent in the evolution of any new science is the slow development of a standard nomenclature. To characterize the behavioral effects of drugs, many terms have been suggested. The one most frequently used is tranquilizer, indicating a sedative or calming effect without induction of sleep. Also common are the terms neuroplegic and neuroleptic which indicate diminutions in the intensity of nerve function, and ataraxic, denoting peace of mind. Other more general terms which indicate that the agent employed has an action on the mind are psychotropic, phrenotropic, and phrenopraxic (Himwich, 1958). It should be emphasized that none of these terms is wholly satisfactory and the meanings of many are ambiguous.

B. Classification of Psychopharmacologic Agents

Currently, drugs that affect mood and behavior can be subdivided into three categories. The ataractics (or tranquilizers) which have the ability to calm hyperactive, agitated individuals without causing marked confusion, drowsiness, or disorientation; the psychomotor stimulants ("psychic energizers") which are used to combat depressive symptoms in both psychoses and neuroses; and the psychotomimetics (hallucinogens) which are useful research tools because of their ability to produce a mental state which resembles a spontaneous psychosis.

The ataractic category embraces a large number of compounds which have been classified by means of chemical structure and clinical indication. According to chemical structure there are four principal groups of these drugs: (1) phenothiazine deri-

vatives, (2) rauwolfia derivatives, (3) propanediol derivatives, and (4) diphenylmethane derivatives. On the basis of clinical indication, the phenothiazine derivatives and the rauwolfia derivatives are considered "major" ataractics in that they are effective in the treatment of both psychoses and neuroses, whereas the propanediol derivatives and the diphenylmethane derivatives are classified as "minor" ataractics because of their usefulness in the treatment of neuroses and anxiety states and their relative ineffectiveness in combating psychoses.

C. Chlorpromazine, the Ataractic Prototype

Among the major ataractics, the phenothiazine derivatives have enjoyed the broadest usage, and, of these, chlorpromazine is considered the prototype. Chlorpromazine is designated chemically as (alpha dimethylaminopropyl) 2-chlorophenothiazine hydrochloride. It is chemically related to promethiazine (Phenergan) and was first investigated for its mild antihistaminic properties. The basic pharmacology of this compound has been reviewed by Killam (1959). Chlorpromazine evokes a multitude of pharmacologic responses in both animals and man. Principal effects include central nervous system depression without hypnosis or anesthesia, good antiemetic action, and mild adrenergic blockade. The drug has the ability to produce a transient initial hyperthermia followed by a more persistent hypothermia. The poikilothermic effects of the drug and its capacity to potentiate the action of anesthetics and sedatives provide further evidence of central activity. As yet, there is no adequate explanation available for the site and mode of action of the tranquilizing effects of the drug.

A recent review of the diagnostic entities for which chlorpromazine has been used (Evarts and Butler, 1959) reveals that a great many different psychiatric disorders are benefited by therapy with this drug. In keeping with its classification as a major ataractic, studies have shown that chlorpromazine causes improvement in schizophrenic reactions, geriatric psychoses, alcoholic psychoses, and the manic phases of manic-depressive psychoses. Other clinical trials have indicated that chlorpromazine brings about improvement in obsessive-compulsive reactions, anxiety states, behavior disorders in children, and a wide variety of other neuroses. The improvement reported usually has been restricted to alleviation of symptoms such as tension, anxiety, hyperactivity, etc.

Although the drug has been reported useful in all of the generally recognized psychiatric "disturbed" conditions (Goldman, 1955), it is generally accepted that certain cases of depression constitute the major psychiatric entity in which chlorpromazine may occasionally be contraindicated. However, its usefulness in several other conditions has been questioned. Thus, chlorpromazine has been said to be without value both in the treatment of personality disorders (Margolis et al., 1956) and in reducing the withdrawal symptoms of narcotic addicts (Fraser and Isbell, 1956).

D. Behavioral Techniques and Their Use in the Evaluation of Chlorpromazine

1. Techniques. One of the major problems facing the area of psychopharmacology is the identification and replication in laboratory animals of behavioral processes which may be analogous to those observed in human maladaptive behaviors. This problem is

relevant not only to the development of more efficacious therapeutic agents, but also has considerable bearing on a better understanding of behavioral relationships. In spite of intensive and systematic efforts to investigate the relations between drugs and behavior, this problem remains largely unsolved. Several recent reviews (Brady, 1959a; Sidman, 1959; Miller and Barry, 1960) which deal with current methods employed in the preclinical assessment of drug activity have mentioned that this involves not one, but a series of interrelated problems.

In addition to the usual questions of reliability, validity, and sensitivity, problems which are inherent in the pharmacologic evaluation of all drugs, procedures in psychopharmacology must be designed also to solve such complex problems as the motivational effects of drugs and drug-behavior interactions. It is known that the behavioral effects of a drug may vary considerably depending upon the parameters employed to establish and maintain the behavior under investigation. For example, in studies involving conditioning, such factors as the intensity or magnitude of reinforcement and the number and distribution of training trials may markedly influence drug activity. Also, drug effects may vary according to the factors which are motivating behavior, e.g., fear induced behavior vs. hunger induced behavior. Because, presently, there is no single behavioral technique which can contend with the various problems cited above, the current solution involves the use of a series of tests intended to measure, over a range of parameters, drug effects on a variety of animal behaviors.

The behavioral techniques employed in the evaluation of ataractics are varied and

numerous. Surveys of the work in this area can be found in several recent reviews (Riley and Spinks, 1958; Brady, 1959b; Hunt, 1961). Broadly, experimental effort has been divided into two categories - the effects of drugs in relation to non-conditioned and conditioned behaviors. Frequently included in the former are procedures concerned with amphetamine aggregation, spontaneous motor activity, and convulsive behaviors, whereas the latter includes a number of diverse techniques and, hence, requires further discussion.

Conditioning methods are often divided into classical and instrumental. Instrumental methods can be further subdivided into respondent and free-operant types. A classical conditioned response fails to obtain reinforcement from the environment; an instrumental response obtains reinforcement. A respondent conditioned response is elicited by an environmental stimulus, whereas free-operant behavior is emitted "spontaneously."

Many animal studies have emphasized the effects of drugs on behavior that is controlled by aversive stimulation. The onset of this type of stimulation is punishing while its termination is rewarding (e.g., electric shock, air blast). One of the most widely used aversively controlled behaviors is that which occurs in instrumental avoidance conditioning. Here, in the presence of a neutral signal (conditioned stimulus-CS) which predicts a noxious stimulus (unconditioned stimulus - US), the animal learns to make a specified response, first to escape the shock (unconditioned response - UR), and later to forestall it (conditioned response - CR). The response required may be climbing a rope, crossing from an electrified to a non-electrified compartment, clinging

to a vertical pole, turning a wheel, pressing a lever, or whatever response is appropriate to the species employed and to the expected motor and psychological effects of the drug.

Another type of conditioning that has been successfully adapted to the study of drug effects is the free-operant response for a food or water reward. This technique was developed by Skinner (1938) who conditioned hungry or thirsty animals to obtain pellets of food or drops of water by making appropriate motor responses (lever pressing, pecking, etc.). The behavior elicited by this procedure is slowly extinguished and is quite stable. The apparatus used in free-operant conditioning has been adapted to include the study of avoidance conditioning (Sidman, 1953). In this method, the animal learns to press a lever to postpone a shock for a specified interval. Shocks are given at regular intervals unless the lever is pressed, thus delaying the appearance of the next shock.

Conditioning techniques have also been used to study the effects of drugs on emotional responses in animals. This method, originated by Estes and Skinner (1941), demonstrates that a previously neutral stimulus can acquire an emotional significance by being paired with an electric shock. Usually the neutral stimulus (clicking sound) is presented for two or three minutes and is followed by a shock. If the conditioned emotional response to this signal is superimposed on a lever pressing habit, lever pressing is inhibited during the signal, and by comparing the rates of response before and during the signal, a quantitative measure of the conditioned emotional response can be obtained. Studies with this technique have been summarized by Sidman (1959) and

Hunt (1961).

2. Evaluation of Chlorpromazine. The results of experiments in which the assay procedures mentioned above have been used to evaluate the behavioral effects of ataractics is the subject of a recent review by Dews and Morse (1961). Examples of data relative to the evaluation of chlorpromazine are presented below.

With respect to effects on non-conditioned behaviors, chlorpromazine has been shown by a number of investigators to decrease the toxicity of amphetamine in aggregated mice (Lasagna and McCann, 1957; Burn and Hobbs, 1958; Swinyard et al., 1959). It has also been demonstrated that chlorpromazine, in keeping with its central nervous system depressant properties, decreases spontaneous motor activity (Cook et al., 1955; Tedeschi et al., 1959a). The effects of chlorpromazine on convulsive seizures induced by electricity, convulsant drugs, or sound have been the subject of a number of investigations. Chlorpromazine has been shown to lower electroshock seizure threshold (Tedeschi et al., 1958; Fink and Swinyard, 1960) and to be ineffective both in preventing maximal electroshock seizures and in altering the amount of pentylenetetrazol necessary to cause convulsions in mice (Swinyard et al., 1959). Working with groups of mice, Plotnikoff and Green (1957) reported that chlorpromazine conferred protection against audiogenic seizures, but Fink and Swinyard (1959) reported that the drug is ineffective in protecting isolated mice against maximal audiogenic seizures.

The influence of chlorpromazine on conditioned behaviors has been studied from many viewpoints. The review of Dews and Morse (1961) provides an excellent discussion of the many approaches employed. Only the more prominent procedures will be pre-

sented herein.

With respect to avoidance conditioning, it has been reported by many workers using a variety of techniques that the response to a warning stimulus (avoidance behavior) is more readily suppressed by chlorpromazine than is the response to a noxious stimulus (escape behavior) (Courvoisier et al., 1953; Cook and Weidley, 1957; Smith et al., 1957; Verhave et al., 1958). Several studies have shown the effects of chlorpromazine on the acquisition and extinction of conditioned avoidance responses. Employing a shuttle box and rats as the experimental animals, Ader and Clink (1957) have shown that chlorpromazine can retard the acquisition of a conditioned avoidance response. These same investigators and Miller et al. (1957) have shown that such a response is also extinguished more rapidly under the influence of this drug.

Several efforts have been directed toward the effect of chlorpromazine on conditioned emotional responses during free-operant behavior. Chlorpromazine has been shown to weaken a conditioned emotional response superimposed upon an instrumental habit in which a rat was trained to run from one end of an experimental chamber to the other for a water reward (Heistad, 1958). Hunt (1956) has also shown that chlorpromazine does not block conditioned emotional responses but weakens them so that the behavior of treated animals is like that of animals conditioned with weaker shocks. He has also observed that chlorpromazine blocks the extinction of such responses in rats.

Based on results obtained with free-operant techniques, Dews (1958) has reported that chlorpromazine does not readily modify behavior which is motivated by certain

types of environmental stimuli (such as reinforcing stimuli, e.g., food).

E. Innate vs. Learned Behavior

1. Classification. From this brief survey of the literature, it becomes apparent that a multi-faceted approach is currently the best means of examining the behavioral effects of drugs. Thus, as discussed above, animal experimental studies in psychopharmacology have been concerned with a multitude of behaviors. However, one aspect of behavioral investigation which has lagged somewhat is that concerned with the effects of drugs on innate action patterns in a variety of species. Both Beach (1950) and Hunt (1961) have indicated the need for more innate behavioral data in a variety of species. These authors have pointed out that the responses generally classified as innate have not been studied as extensively or intensively as problem-solving behavior, and, consequently, the effects of drugs on these innate patterns remain largely an enigma.

Perhaps the major reason for the lack of psychopharmacologic data on innate responses can be found upon examination of the chief source of the discipline's techniques. It is well-known that psychopharmacology has borrowed freely from behavioral techniques developed in the area of experimental psychology. For many years, psychologists, in the pursuit of objective experiments which could be carried out under rigorously controlled conditions, have stressed learning and conditioned behaviors. This search for objectivity led to the development of behavioral theories and techniques which were almost invariably designed to study learning and conditioning. However, as

Eibl-Eibesfeldt (1958) has pointed out, "The validity of conclusions drawn from learning and conditioning experiments, however carefully 'controlled,' when carried out without knowledge of the animal's innate behavior, is often open to considerable question." In spite of this admonition, psychopharmacologists have proceeded to evaluate drug activity on the basis of learning and conditioning while essentially neglecting the innate response patterns of the experimental subjects.

It is frequently difficult, however, to classify behavior into two distinct categories, innate and learned. Fuller and Thompson (1960) have commented on this dichotomy and have stated that, carried to its logical conclusion, innate behavior would be defined as that which appears in the absence of environment and learned behavior as that which requires no organism. Verplank (1955) has also called attention to the complexities of this problem in stating, "We can no more distinguish between behavior that is learned and behavior that is innate than physicists can distinguish between light that is made up of transverse vibrations and that which is made up of corpuscles. Innate and learned must always be assumed to have quotation marks about them." In view of these observations, it would appear pertinent to discuss in more detail what is meant by innate behavior.

Innate or instinctual behavior in genetic terms is behavior so highly determined by genes that it occurs uniformly under practically any condition which will permit survival. The evidence is strong that heredity plays a large part in the determination of a great many kinds of traits in a wide range of species; however, the exact character of the relationship between nature and nurture is by no means settled, and, therefore,

a rigid distinction between innate and learned components of behavior is difficult and arbitrary.

In an attempt to account for the variation between individuals, Dahlberg (1953) has classified the characteristics of an organism as follows: (1) A trait is called hereditary if most of the variation within a population is associated with differences in genetic endowment, e.g., blood type. (2) A non-hereditary or acquired trait has little or no genetically determined variance, e.g., customs and language. (3) Variation in this group of traits is significantly affected by both genetic and environmental factors. Skin color, body size, and most characteristics which vary quantitatively over a wide range belong in this "interaction" category.

Most behavioral traits involve both genetic (innate) and environmental (learned) determinants and fall into Dahlberg's "interaction" category. Thus, the organism's behavior is a joint function of its genes and its past environmental interactions. While the terms "innate behavior" and "learned behavior" will occasionally be used throughout this thesis, it should be kept in mind that both of these terms refer to "interaction behaviors." The real problem is to determine the relative contribution of genetic vs. environmental determinants in specific behavioral traits.

Currently, little is known of the proportional contribution of hereditary and environmental factors to observed individual differences in behavior. As Anastasi (1958) has pointed out, "The proportional contribution of heredity to the variance of a given trait, rather than being a constant, will vary under different environmental conditions. Similarly, under different hereditary conditions, the relative contribution

of environment will differ." However, if one examines the development of behavior patterns phylogenetically, it becomes evident that genetic determinants play a very large role in the expression of specific behaviors in the lower forms of life. This is readily apparent in the case of insects. For example, ants have solved the problem of environmental adaptation by existing in colonies which are socially organized on the basis of morphology and behavior into distinct classes. Both the behavior and the morphology of the individuals within these groups is genetically determined so that an ant which is classified as a "worker" will never exhibit the behavior which is characteristic of one classified as a "fighter" and vice versa. Because of this, these organisms are limited in the scope and complexity of their behavioral patterns, and those behaviors which they do possess are often characterized by a fixed rigidity of response to any specific stimulus. It also can be clearly seen that learning is excluded from specific behavior patterns of certain other insects. For example, courtship behavior, which occurs on the first meeting of an adult male spider with a receptive female, inhibits their usual predatory and self-protective behavior. Moreover, in some species, it undoubtedly prevents the male from being eaten by the female before copulation. In this situation, there is obviously no time for learning appropriate responses, and, hence, the behavior must be genetically determined.

As one ascends the phylogenetic tree, the influence of genetics upon behavior is modified by learning and, therefore, becomes less obvious, whereas the behaviors themselves become more complex. For example, the correlation between genetic

factors influencing behavior and the form in which such behavior is expressed in the adult animal is less precise in mammals than it is in insects. This represents a greater behavioral repertoire enjoyed by the individual animal, the increasing complexity of its nervous system and capacity for learning, and, accordingly, a greater intervention of experience in the organization of its behavior. Thus, a transition occurs from genetically determined behaviors which are characterized by a fixed rigidity of response, e.g., insects, to genetic-learned interaction behaviors which are characterized by a lability of response, e.g., mammals.

The only conclusions that can be drawn relative to mammalian behaviors seem to be that both heredity and environment contribute to all behavior traits and that the extent of their respective contributions cannot be wholly defined for any trait.

Several mammalian behaviors are known to be dependent upon genetic determinants for the initial expression of a response and upon environmental determinants (learning and experience) for full development of the response. For example, maternal behavior in rabbits is known to be genetically determined and usually includes a nest building phenomenon. The results of Sawin and Crary (1953) indicate that early building and high quality of nest are correlated with a high per cent of survival in the newborn. It has also been shown that the quality of nest building often improves with each succeeding litter and is thus markedly influenced by learning. Maternal behavior in rats is known also to be genetically determined and usually includes nest building and the retrieving of pups. Lehrman (1953) has speculated, however, that adequate nest

building and retrieving responses are dependent upon the experience gained in handling and manipulating solid objects. This speculation was based on the work of Riess (1954) in which rats were raised in isolation and provided with only powdered food so that these animals had no opportunity to handle solid objects. Following mating, these animals were then placed in cages which had an adequate supply of nesting material and their maternal behavior was observed. It was noted that none of the rats built nests and that a large mortality rate occurred because of a decreased tendency to retrieve the scattered pups. As a final example, the hoarding behavior of rats has been shown to be determined not only by genetic factors, but also by the deprivation state of the animal and its early experience with transportable objects (Stamm, 1954; Holland, 1954).

Behaviorists and geneticists generally agree that in mammals the adaptive nature of behavior is largely insured through the process of learning. Genetic variation, however, is known to provide a second mechanism for adjusting to different environmental conditions. Because of the large amount of experimental effort directed toward examining adaptive behaviors, it might be presumed that behaviors which are innate have been as thoroughly studied as those which are learned. However, the majority of this work has been conducted in the realm of psychology, and,for reasons mentioned previously, this discipline has chosen to ignore innate response patterns.

Although ethologists have stressed innate behavior, they have concerned themselves largely with species-specific behavior in birds, fishes, and insects. Ethological studies involving mammals are quite rare and, for the most part, are unrelated to the theme

of this thesis. One exception is the work of King (1958) dealing with differences in the rates of development of behavior and in the frequency of specific response patterns in two subspecies of the deermouse Peromyscus maniculatus.

2. Drug Research in Innate Behaviors. In spite of the recognized need for studies involving innate behaviors (Beach, 1950; Fuller and Thompson, 1960; Hunt, 1961), comparatively little drug research has been directed along these lines. Much of what little has been done deals with hormonal effects on sexual and maternal behavior. How these drugs alter such apparently innate behavior patterns is discussed by Brady (1959b) in a review of comparative psychopharmacology. Testosterone has been shown to stimulate precocious sexual behavior in young male rats (Stone, 1940; Beach, 1942a), and to arouse sexual activity in senile (Minnick et al., 1946) and castrated animals (Beach and Holz, 1946). The injection of estrogen into young female rats results in precocious sexual behavior (Beach, 1942b), whereas a combination of estrogen and progesterone has been shown to produce normal sexual patterns in spayed virgin females reared in isolation (Beach, 1942b). Riddle et al. (1935, 1942) have shown that maternal behavior (nest building and retrieving of young) can be induced in virgin female rats following the administration of prolactin. The extent to which non-hormonal substances might produce comparable alterations in such innate responses remains to be elucidated by chronic, systematic experimentation.

The work of Zimbardo and Barry (1958), which demonstrated that chlorpromazine can depress sexual activity in male rats, represents one of the few attempts to evaluate the effects of ataractics on this type of innate response.

Employing an avoidance conditioning paradigm, Sacra et al. (1957) have made use of a seemingly innate behavioral characteristic of cats. Cats with a natural tendency to attack mice are conditioned by being given an electric shock every time they attempt to pick up a mouse. This procedure rapidly produces a stable mouse-avoidance behavior. Under the influence of chlorpromazine and other ataractics, cats so trained will continue to pick up the mouse again and again although dropping it when shocked.

Non-mammalian, genetically determined behaviors which have been used in evaluating ataractics include the web-spinning behavior of spiders (Witt, 1956) and the fighting response of the Siamese fighting fish, Betta splendens (Walaszek and Abood, 1956). However, it is difficult to extrapolate the results obtained to mammalian psychopharmacology.

F. Statement of the Problem

By and large, the experimental efforts directed toward examining the effects of ataractics upon innate behaviors have often been cursory, and the results obtained in the works cited above have, in many cases, been controversial and difficult to interpret. In view of these observations and the generalized paucity of pertinent information, it was thought that a systematic evaluation of the effects of chlorpromazine on innate vs. learned behavior might reveal worthwhile information. In order to determine the particular behaviors to be studied, a variety of rodent species were reviewed in terms of information relative to their ecology and "natural" behavior patterns. It was evident that there were striking differences in behavior between and within the species examined,

and, in many instances, there was a strong correlation between the ecology of the species and the overt response patterns displayed by the animal. Because of the pressures of natural selection, it was anticipated that such ecologically-influenced behaviors would be characterized by a minimum of individual variability and a high degree of stability. It was also thought that these behavioral patterns could be replicated in the laboratory, if experimental apparatus and procedures were specifically designed, a priori, to provide stimulus conditions and response opportunities favorable to the expression of such behaviors. Furthermore, it was anticipated that certain quantitative aspects of the behavior elicited by these experimental procedures, in contrast to that elicited by procedures not involving such specific design features, might be correlated with the behavioral genotype of the animal under investigation.

The expectations cited above can best be exemplified in hypothetical terms. If the behaviors selected are predominantly influenced by genetic determinants, as opposed to environmental determinants (learning and experience), then, in an appropriate experimental situation, the former should be (1) more rapidly acquired, (2) more slowly extinguished, and/or (3) more resistant to modification by psychopharmacologic drugs. The experiments to be described were designed to test these hypotheses.

II. GENERAL PROCEDURES

The experimental animals used in these studies were adult male and female mice of the genera Peromyscus and Onychomys. Specifically, the animals employed were (1) Peromyscus maniculatus gracilis (woodland deermouse), (2) Peromyscus maniculatus bairdi (prairie deermouse), and (3) Onychomys leucogaster (northern grasshopper mouse). The two subspecies of deermouse were obtained from the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine; the grasshopper mice were obtained from Dugway Proving Grounds, Dugway, Utah.[1] All animals were allowed free access to food (Rockland Rat Diet supplemented with wheat) and water except during actual test procedures.

The animals were segregated with respect to sex and were housed in standard (model 103) Keystone plastic cages. To prevent overcrowding, no more than 8 animals were housed in each cage. Since grasshopper mice may fight and kill one another when housed collectively, these animals were quartered in the individual compartments of a standard Keystone cage which had been subdivided into fourths by metal partitions.

Because several of the behavioral tests used in this study are based upon ecological assumptions, and, in view of the fact that these rodents differ in many aspects from conventional laboratory mice, a brief description of each animal group is included.

The woodland deermouse (P.m. gracilis), with its large ears, pure white belly,

[1]The author would like to thank Dr. John A. King and Mr. Frederick Hart of Hamilton Station, Roscoe B. Jackson Memorial Laboratory, and Mr. Harold Egoscue, Department of Ecology and Epizoology Research, University of Utah, for their help in supplying experimental animals.

and rich, fulvous upper parts is a striking, small mammal. Its long tail is distinctly bicolored, white below and brownish above. This rodent is an inhabitant of heavy woods; a typical habitat is the northeastern hardwood forests (Hooper, 1942). Although mainly terrestrial, these mice readily climb trees. Some of their stores of food as well as nests may be in holes in trees or stumps (Burt, 1957).

The prairie deermouse (P.m. bairdi) is considerably smaller than the woodland deermouse. Its upper parts are usually grayish-brown, lacking the bright, fulvous pelage of gracilis. Its tail is shorter than that of gracilis and is distinctly bicolored, white below and gray above. This mouse inhabits treeless areas, such as natural prairies, from Michigan west to North Dakota and south to Ohio and Oklahoma (Osgood, 1909). It is also common on open lake beaches (Dice, 1925). This is truly a grassland species. The nest is in a ground burrow made by the mouse or appropriated from some other animal that has no further use for it (Burt, 1957).

In the laboratory, these two races of deermouse exhibit striking differences in behavior (Foster, 1959). The prairie-inhabiting race, bairdi, appears to be hyperexcitable and is difficult to handle, whereas the forest-inhabiting race, gracilis is more placid and is easily handled.

The northern grasshopper mouse (Onychomys leucogaster) is stocky, with a short, thick tail as compared with the long, slender tail of the deermouse. Its pelage is bicolored; grayish or blackish-brown to reddish-brown upper parts, abruptly changing to pure white under parts. The animal inhabits sandy sagebrush country, as well as short-grass areas throughout most of western North America. It generally avoids the hot,

low deserts of the arid Southwest (Cahalane, 1947). This mouse commonly nests in a ground burrow.

Most rodents eat mammal carcasses, but the grasshopper mouse is an accomplished carnivore. It has keen senses and is a persistent trailer. This short-legged, stout little mammal stalks its prey and, then, with a rush, seizes it and kills by slashing its teeth into the base of the victim's brain. Preceding and during an attack, this animal often utters a succession of sharp, squeaking barks. The grasshopper mouse is not totally dependent on warm-blooded prey for its existence, since insects and seeds are also included in its diet.

The weight of the experimental animals used in these studies varied as follows: P.m. gracilis - 22 to 30 g.; P.m. bairdi - 16 to 24 g.; and O. leucogaster - 25 to 34 g.

The psychopharmacologic agent employed throughout these studies was chlorpromazine hydrochloride (Thorazine Hydrochloride). The drug was administered intraperitoneally in aqueous solution in such concentration that 10 ml./Kg. body weight of the solution contained the appropriate dose of the drug.

Behavioral trials were conducted at the time of peak drug activity. This was determined in all species by a series of neurological toxicity tests conducted at 15, 30, 60, 90, and 120 minutes after administration of chlorpromazine. All animals were examined for neurological abnormality as evidenced by loss of righting reflex, loss of placing reflex, abnormal body posture, or ataxia. In addition to the measures of neurotoxicity cited above, the following two tests were also used to estimate motor in-co-ordination; the rotating rod and the inclined plane tests. The rotating rod test measures the inability

of a mouse to maintain equilibrium for 1 minute on a horizontal plastic rod (diameter, 1 in.; rough finish) rotating at 6 revolutions per minute and was used as a more precise measure of neurotoxicity in P.m. gracilis. This test was unsuitable for the other two species; P.m. bairdi will not remain on a rotating rod, whereas O. leucogaster has difficulty in getting all four feet on the rod. Hence, the inclined plane test, which measures the inability of a mouse to maintain motor co-ordination when allowed to run down the rough side of an inclined plane (Masonite; slanting approximately 33^{o} from horizontal), was used as a more precise measure of neurotoxicity in these two species. Preliminary studies indicated that neurological deficit as detected by the rotating rod test correlates well with that detected by the inclined plane test. The time of greatest neurological deficit was taken as the time of peak drug effect. By means of these procedures, the dose of chlorpromazine which produced overt evidence of minimal neurotoxicity in 50% of mice (TD_{50}) was determined for each species.

In order to determine the TD_{50}, groups of 6 to 10 mice (males and females) were given various doses of drug until at least 3 points were established in the range between 0 and 100% minimal neurotoxicity. Careful observation of these animals revealed that sex had no apparent bearing on the toxicity of chlorpromazine. The results were plotted on logarithmic probability paper and a regression line was fitted to the plotted points by eye. From this plot of the data, the TD_{50} was estimated and the 95% fiducial limits were calculated by the method of Litchfield and Wilcoxon (1949).

The times of peak activity and the mean neurotoxicity (TD_{50}) for chlorpromazine in mice are summarized in Table 1. For comparative purposes, similar data obtained in a conventional laboratory mouse (Carworth Farms; CF #1 strain) are also included.

TABLE 1

THE TIMES OF PEAK EFFECT AND MEAN NEUROTOXICITY (TD_{50}) OF CHLORPROMAZINE IN MICE

Animal	Time of Peak Effect (minutes)	TD_{50} (mg./Kg.)
Peromyscus maniculatus gracilis	60	16.0 (11.0 - 23.2)*
Peromyscus maniculatus bairdi	60	18.2 (13.8 - 24.0)
Onychomys leucogaster	60	12.8 (9.5 - 17.3)
CF #1	60	5.0 (2.7 - 9.4)

*Values in parentheses represent 95% fiducial limits.

III. THE EFFECT OF CHLORPROMAZINE ON TWO TYPES OF AVOIDANCE BEHAVIOR

A. Introduction

Avoidance behavior may be defined as behavior that occurs in the presence of originally neutral stimuli which have been associated in the past with a succeeding aversive stimulus; such behavior has as its consequence the prevention or postponement of the aversive stimulus (Dews and Morse, 1961). Whenever avoidance conditioning paradigms are used, animals learn to react to a warning auditory or visual stimulus (conditioned stimulus, CS) in order to forestall or prevent the appearance of an aversive stimulus (unconditioned stimulus, US). To avoid the US, the animals must make some arbitrary response which is designated as the conditioned response (CR). In contrast, escape behavior is behavior which occurs during the presentation of the US and which has as its consequence the cessation of such stimuli. The response made by the animal in this situation is designated as the unconditioned response (UR).

Many of the commonly employed conditioned avoidance techniques are modifications of a method originally proposed by Warner (1932) in which experimental animals were trained to respond to a CS by hurdling a low barrier in a two-compartment shuttle box. Included in this category are all those conditioning techniques in which the experimental animal, once placed in a shuttle box, must find a "safe area" (pan, ledge, etc.) in order to avoid the US. The "pole climbing" response of Cook and Weidley (1957) in which rats are trained to climb a vertical pole upon presentation of the CS is representative of a complex modification of Warner's original technique.

In the conditioned avoidance paradigms cited above, the responses required of the

experimental animals must be considered learned rather than innate in that no attempt is made to condition a genetically acquired escape behavior. Rather, effort is directed toward channeling the random escape movements of the animals, brought on by the US, toward the appropriate solution, e.g., jumping a barrier or climbing a pole. Once this type of escape response has been elicited in an animal, a conversion to avoidance behavior is relatively easy and the avoidance response becomes very consistent.

It has been known since the early work of Courvoisier et al. (1953) that chlorpromazine suppresses avoidance behavior more readily than it does escape behavior. The differential suppression of such activity has served as the basis for many conditioned avoidance tests designed to evaluate potentially useful ataractics. Several investigators have demonstrated that chlorpromazine can block the "shuttle box" type of CR in doses which do not significantly suppress the animal's UR (Nielsen and Neuhold, 1959; Irwin et al., 1959; Fink, 1960). Also, the ability of chlorpromazine to interfere selectively with a conditioned pole climbing response has been repeatedly confirmed by many workers (Cook and Weidley, 1957; Piala et al., 1959; Swinyard et al., 1959; and others). On the other hand, comparatively little is known of the effects of drugs on avoidance behaviors which result from conditioning genetically determined escape patterns. Therefore, it was thought profitable to compare in an appropriate species the effects of chlorpromazine on innate vs. learned conditioned avoidance behavior.

P.m. gracilis was selected as the experimental animal for a number of reasons. It is a semi-arboreal animal which spends part of its life on the trunks and branches of

trees and shrubs. Several studies have shown that this race of deermouse is well-adapted to an arboreal habitat. Horner (1954) has observed that the long tail of gracilis serves not only as a prehensile organ, but also helps the animal to maintain balance when climbing. King (1958) and King and Shea (1959) have demonstrated that gracilis matures very rapidly with respect to clinging and climbing abilities.

Since this animal is familiar with arboreal environments, and because its buffy coloration is well-adapted for concealment on tree branches, it is not unreasonable to assume that this animal will seek an arboreal means of escape when threatened by certain predators. Since escape patterns are of primary survival value to any organism, it may also be assumed that these patterns are "built-in" genetically and, hence, innate.

In view of these observations and assumptions, a series of experiments were designed to compare the avoidance behavior of P.m. gracilis in a situation which demanded an arboreal solution with its avoidance behavior in a situation which demanded a terrestrial solution. Specifically, a comparison was made of the acquisition and extinction, as well as the acute effects of chlorpromazine on avoidance behavior in which the appropriate CR was climbing a vertical pole (arboreal response) with avoidance behavior in which the appropriate CR was remaining on a "safe area" pan (terrestrial response).

It was hypothesized that, in this species, a conditioned arboreal response would be more readily acquired, less readily extinguished, and less susceptible to drug effects than would a conditioned terrestrial response.

B. Methods

The experimental subjects were 48 male and female mice of the subspecies

Peromyscus maniculatus gracilis. The animals were all adults and were housed according to sex (6 animals/cage). Before conditioning commenced, the animals were randomly divided into two experimental groups of 24 animals each (12 males and 12 females). One group, hereafter referred to as pan responders, was trained to produce a terrestrial conditioned avoidance response, which consisted of finding and remaining on a "safe area" pan, whereas the other group, hereafter referred to as pole responders, was trained to produce an arboreal conditioned avoidance response, which consisted of finding and climbing a vertical pole.

The apparatus employed to evaluate the terrestrial (pan) response consisted of a shuttle box with a starting section at one end and a "safe area" pan close to the opposite end (Figure 1). The shuttle box, made of clear Plexiglass, was 28 in. x 4 in. x 8 in. high, with a grid floor composed of stainless steel rods (1/8 in. diameter, placed 1/4 in. apart) through which an electric shock (60-cycle alternating current; 25 volts, delivered through a grid scrambler) could be applied to the feet of the mouse. The box was closed at the top by a clear Plexiglass cover in order to retain the mouse within the apparatus and still permit observation. The starting section consisted of an area of approximately 8 square in. formed by placing a sliding door 2 in. from the front end of the box. The "safe area" pan, constructed from a thin plate of stainless steel, was hinged so that it would be depressed slightly (1/4 in.) under the weight of the mouse. This area, which was located 22 1/2 in. from the front of the shuttle box, was 4 in. wide and extended for a distance of 2 3/4 in. toward the rear of the box. Thus, the grid floor

extended an additional 2 3/4 in. beyond the end of the "safe area" pan to the rear wall of the shuttle box. An electric buzzer was placed beneath the grid floor and served as the source for the CS. The onset of both buzzer and shock was manually controlled.

The same apparatus as described above was modified as indicated below and used to evaluate the arboreal (pole) response (Figure 2). The pan area was blocked off, making the over-all dimensions of the shuttle box 22 in. x 4 in. x 8 in. high, and an aluminum pole (1/2 in. diameter; scored) was suspended from the cover of the box to 1 in. above the grid floor. This pole was located 20 in. from the front of the shuttle box and offered the only route of escape from the electrified grid floor.

The mice were trained to respond to the buzzer (CS) and thus avoid shock (US) by finding and remaining on either the pan or the pole for a period of at least 5 seconds. In both response situations, the following conditioning scheme was employed: a mouse was placed in the starting area and a GraLab electric timer was started. At the end of 5 seconds, the door separating the starting area from the rest of the shuttle box was elevated, and the mouse was given 5 seconds exposure to the environment. Following this, the buzzer was activated for 15 seconds. If an avoidance response was not made within this interval, the buzzer remained on and an electric shock was applied to the feet of the animal through the grid floor. The buzzer and shock were continued until the animal made the appropriate escape response or until a total period of 60 seconds had elapsed; whereupon the buzzer and shock were terminated and the animal removed from the box. Very few animals required more than 5 seconds of shock to produce an

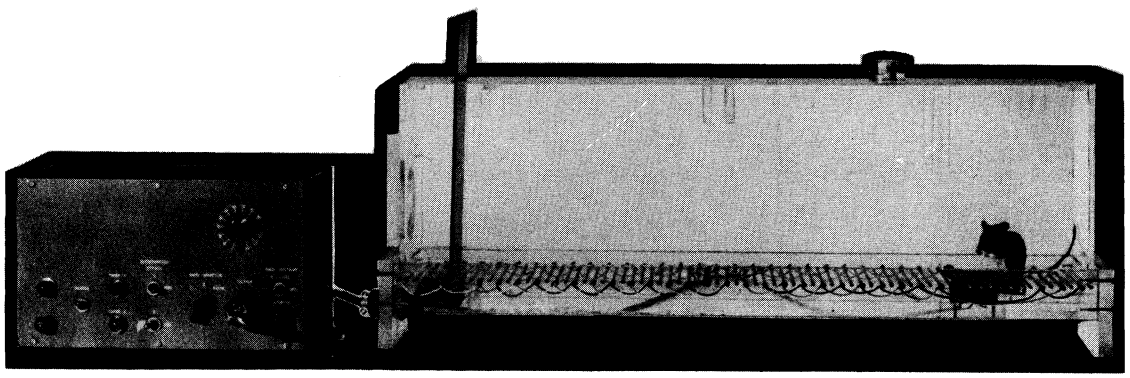


Fig. 1.- CONDITIONED AVOIDANCE (PAN) APPARATUS

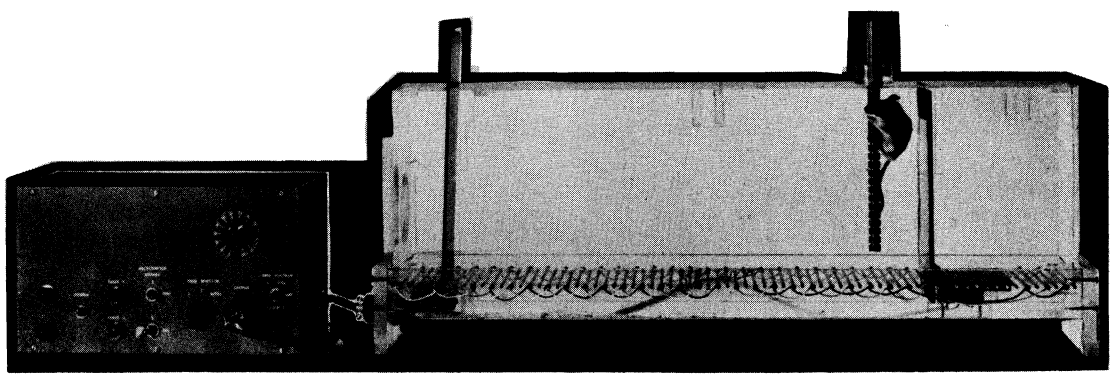


Fig. 2.- CONDITIONED AVOIDANCE (POLE) APPARATUS

escape response. Each 60-second (maximum) sequence (5 seconds start box, 5 seconds environment, 15 seconds buzzer, and up to 35 seconds buzzer and shock) constituted one training trial, and each animal received 8 such trials per day at the rate of 4 trials per 5 minutes.

To determine the rate of acquisition of the two avoidance responses, both experimental groups were subjected to 48 conditioning trials (8 per day for 6 days). If an animal made only one escape response out of 8 trials or if it failed to make at least 6 consecutive avoidance responses in 32 trials, conditioning was discontinued; two animals were dropped from the study for failing to meet these criteria. Two other animals died during the course of the study which reduced the total population of the sample to 44.

The total number of CR's which occurred during the 48 conditioning trials was recorded and the accumulated data examined for differences which might exist between pan responders and pole responders. Since both males and females were to be used throughout this study, it was thought necessary to determine the extent to which sex influenced avoidance behavior. Therefore, the results obtained were analyzed for the method of avoidance, sex, and method of avoidance-sex interaction with a 2 x 2 factorial analysis of variance.

To determine the rate of extinction of the two avoidance responses, 12 mice from each of the two experimental groups were randomly chosen from a selected population. This population consisted of all those animals which had reached a conditioning criterion of at least 6 consecutive avoidance responses in their last 8 trials. Thus, the animals

used to study extinction were chosen from among the best responders in the acquisition study. To ensure that both experimental groups started the study at the same conditioning level, all mice were conditioned to a criterion of 8 consecutive avoidance responses (100%). At the end of each day's trials, any animal not achieving this standard was given 4 reinforced trials (CS and US activated simultaneously). Extinction trials were begun on the day after an animal demonstrated that it had reached conditioning criterion.

The procedure during extinction was similar to that during conditioning except that the US was eliminated. The animals were given 9 days of extinction trials in blocks of 8 trials per day. The first 3 blocks of trials were conducted daily, whereas 48 hours were allowed to elapse between the remaining trial blocks. The measure recorded during extinction was the number of failures to respond to the CS. In order to determine if true differences existed in the extinction rates of pan responders vs. pole responders, the results obtained were analyzed by means of a group comparison "t" test.

To evaluate the acute effects of chlorpromazine on the two avoidance responses, the 24 animals used in the extinction study were reconditioned to a criterion of 6 consecutive conditioned responses in 8 trials.

It had been observed previously that many animals were readily trained to a point where they exhibited the CR before the presentation of the CS, i.e., they developed a secondary conditioned response (SCR; Maffii, 1959) induced by the environment. To take advantage of these differential levels of conditioning, and as an aid in evaluating

the effects of chlorpromazine, a scoring system was devised which arbitrarily rated the animal's avoidance behavior. The response of each mouse was graded and recorded as follows: a mouse exhibiting an SCR (response to 5 seconds of environment) was assigned 4 points; one exhibiting a CR (response to 5 seconds of environment and 15 seconds of buzzer) was assigned 3 points; one exhibiting a UR (response to 5 seconds of environment, 15 seconds of buzzer, and up to 35 seconds of shock associated with the buzzer) was assigned 2 points; and non-responders were assigned 1 point. The method by which this point system is used to evaluate the behavioral effects of chlorpromazine is described below.

For the determination of drug effects, the two experimental groups (12 pan responders and 12 pole responders) were each randomly divided into two treatment groups: 6 chlorpromazine-treated animals and 6 saline-treated animals (controls). Each drug-treated group was given 2 mg./Kg. (1/8 TD_{50}) of chlorpromazine and each control group was given the requisite volume of 0.9% saline. At the time of peak drug activity, all mice were subjected to 4 conditioned avoidance trials, the response noted, and the total points recorded. A fully conditioned, saline-treated mouse would score 16 points for a block of 4 trials. Forty-eight hours later, all animals in both experimental groups were again subjected to conditioning trials. When the animals had been reconditioned to criterion, the treatment assignments were reversed, i.e., the animals previously given chlorpromazine were given 0.9% saline and those previously given saline were given 2 mg./Kg. of chlorpromazine. Thus, at the end of the experiment, a score was

available which reflected the behavior of every animal in both experimental groups while under the influence of chlorpromazine vs. saline; therefore, each mouse served as its own treatment control. This cross-over design was used so that an evaluation could be made of the ability of chlorpromazine to interrupt both types of avoidance behavior. Once this information was obtained, the extent of drug interference in the pan response was critically compared with that in the pole response. This entire experimental procedure was repeated using a dose of 4 mg./Kg. (1/4 TD_{50}) of chlorpromazine in the drug-treated group and the requisite volume of 0.9% saline in the control group.

The data concerned with the behavioral effect of chlorpromazine vs. saline were statistically analyzed by the Wilcoxon Matched-Pairs Signed-Ranks Test (Siegal, 1956), whereas the data dealing with the differential effects of chlorpromazine on arboreal vs. terrestrial methods of avoidance were statistically analyzed by the Mann-Whitney U Test (Siegal, 1956).

C. Results

The acquisition of the two avoidance responses, as a function of time and trials, is shown in Figure 3. As shown in the Figure, the total population of pole responders exhibited a higher level of conditioning throughout the experiment than did the total population of pan responders. At the end of 48 trials, both experimental groups had apparently reached a plateau at which point the pole responders were performing at a level of 78% CR's, whereas the pan responders were performing at a level of 56% CR's.

For comparative purposes, the acquisition curves of the 24 animals later used in the extinction study (selected population) are also included in Figure 3. This Figure shows that the curves for the selected population are qualitatively similar to those representing the total population but demonstrates that a higher level of conditioning existed in the former. Thus, at the end of 48 trials, the selected group of pole responders and pan responders exhibited the appropriate CR 94% and 80% of the time, respectively.

Over-all analyses of variance revealed that the total number of CR's achieved by the two experimental groups (pan responders vs. pole responders) differed significantly ($P < .01$) for the selected as well as the total population. The sex of the animal had a negligible effect on the results; likewise, the methods of avoidance-sex interaction was also insignificant.

The results of the extinction study are illustrated in Figure 4, from which it can be seen that the rate of extinction is essentially the same in both groups subjected to daily trials for 3 days. However, a difference in the extinction rates appears by day 5 when the interval between trials was extended to 48 hours and reaches a maximum by day 15. Thus, at the end of 24 extinction trials, the mean level of CR's was 91% for pole responders and 93% for pan responders, whereas, after 32 extinction trials, the mean level of CR's for pole responders was 93% and the corresponding value for pan responders was 85%. This divergence continued until, at the end of 72 trials, the pole responders exhibited CR's 84% of the time, whereas the pan responders displayed CR's only slightly

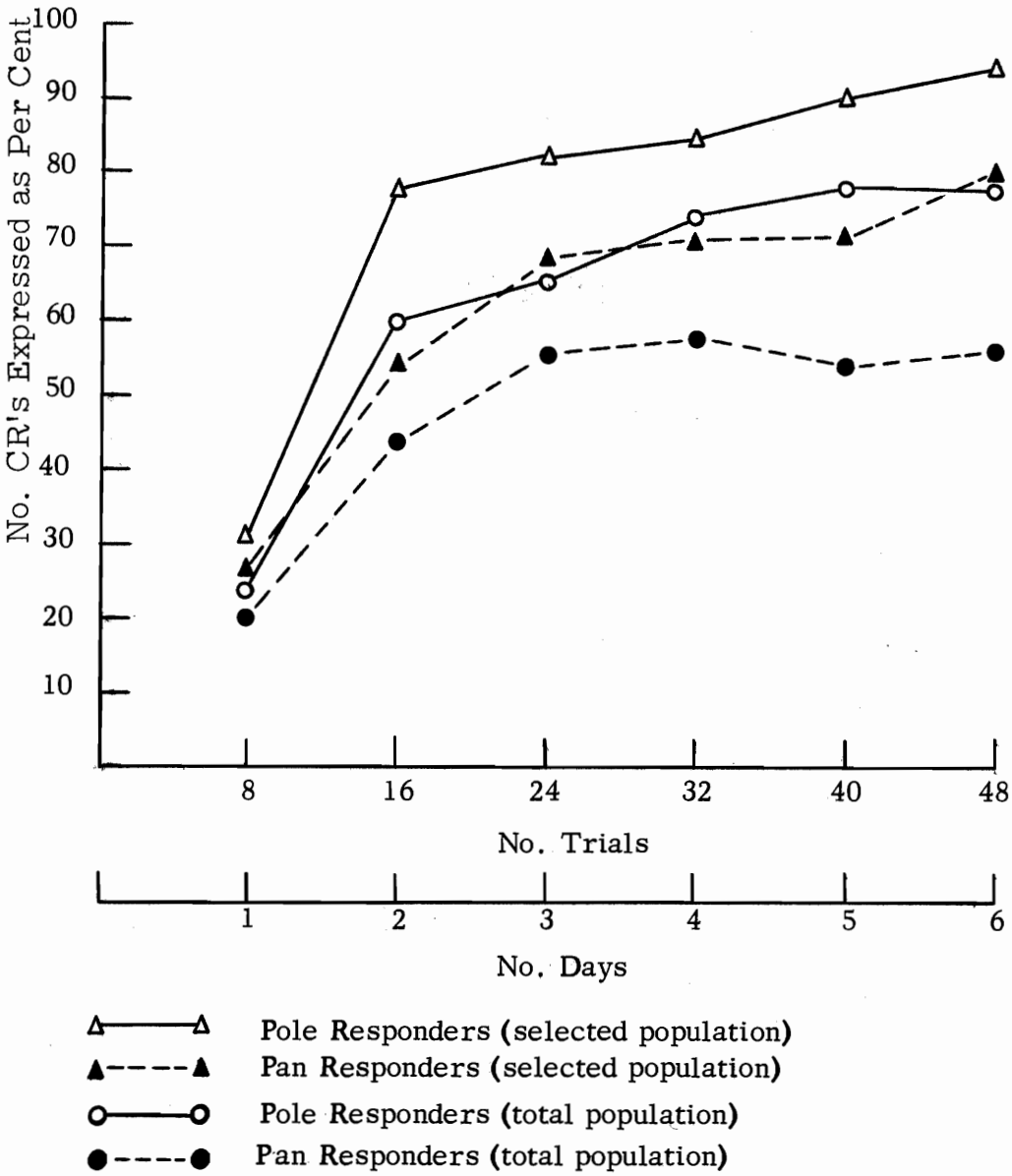


Figure 3. Acquisition of conditioned avoidance responses (CR's) in Peromyscus maniculatus gracilis .

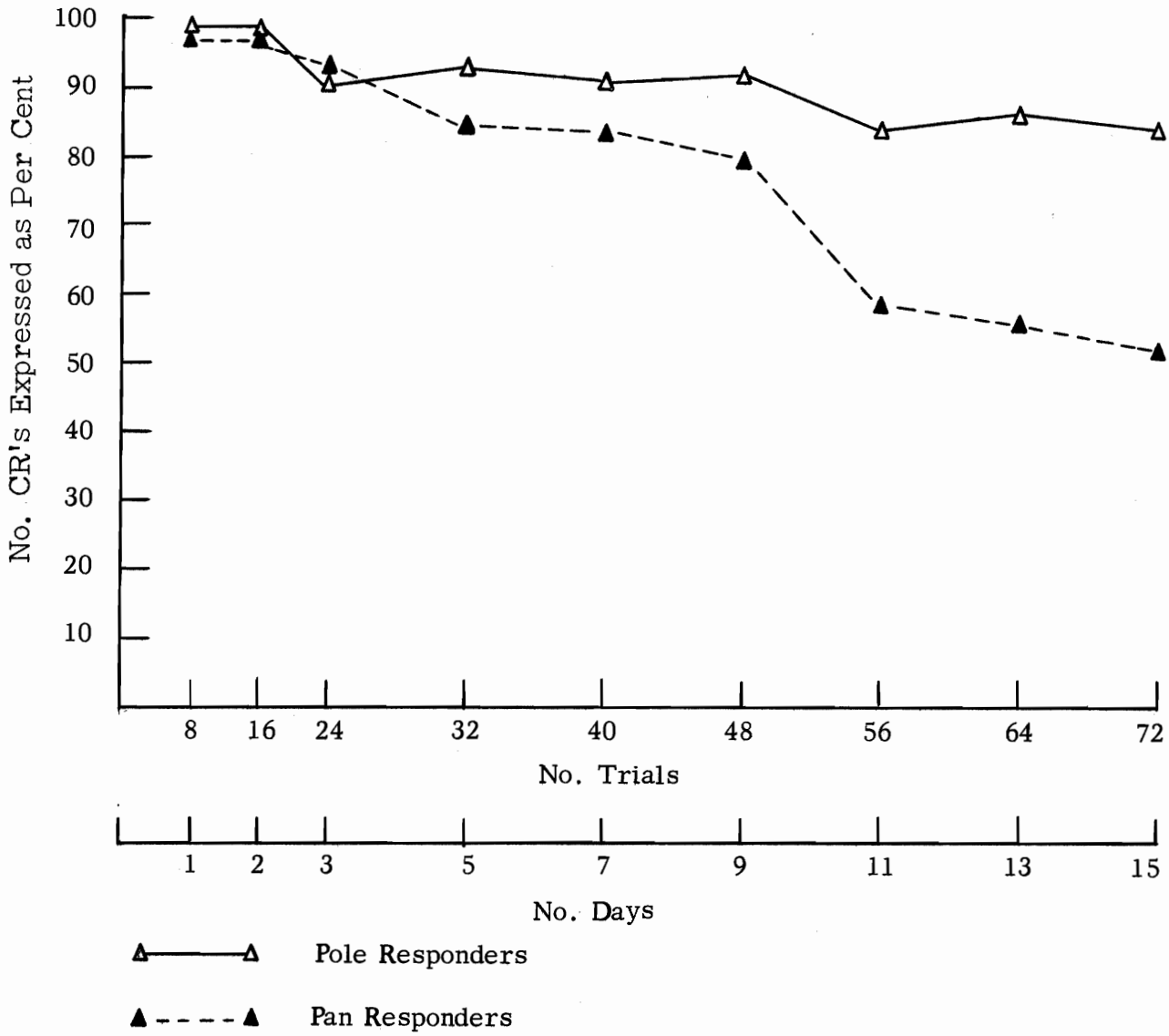


Figure 4. Extinction of conditioned avoidance responses (CR's) in Peromyscus maniculatus gracilis.

more than half the time (52%). A statistical comparison of the last 48 extinction trials revealed that the pan responders had undergone significantly more extinction than had the pole responders ($P < .05$).

The effect of chlorpromazine (2 mg./Kg.) on the two avoidance responses (pan and pole) is illustrated in Figure 5. This dose of chlorpromazine significantly depressed the pan response (saline vs. chlorpromazine; $P < .005$) but had no significant effect on the pole response (saline vs. chlorpromazine; $P > .05$). Also, it can be seen that the extent to which this dose of chlorpromazine interfered with avoidance behavior was significantly greater in pan responders than in pole responders (Δ_1 vs. Δ_2; $P < .05$).

The effect of a 4 mg./Kg. dose of chlorpromazine on the same avoidance responses as described above is illustrated in Figure 6. At this dose level both pan and pole response was significantly reduced (saline vs. chlorpromazine; $P < .005$). However, the magnitude of this reduction was significantly greater for pan responders than it was for the pole responders (Δ_1 vs. Δ_2; $P < .025$).

D. Discussion

The data obtained in these studies emphasize the feasability of conditioning, in the laboratory, a behavior which is known to occur in nature and which is assumed to be predominantly dependent upon genetic determinants (arboreal escape; pole response). The data also show that if the animal is placed in an experimental situation which deprives it of the opportunity to express its natural avoidance behavior, it can be conditioned to forestall a noxious stimulus by producing an avoidance response which is

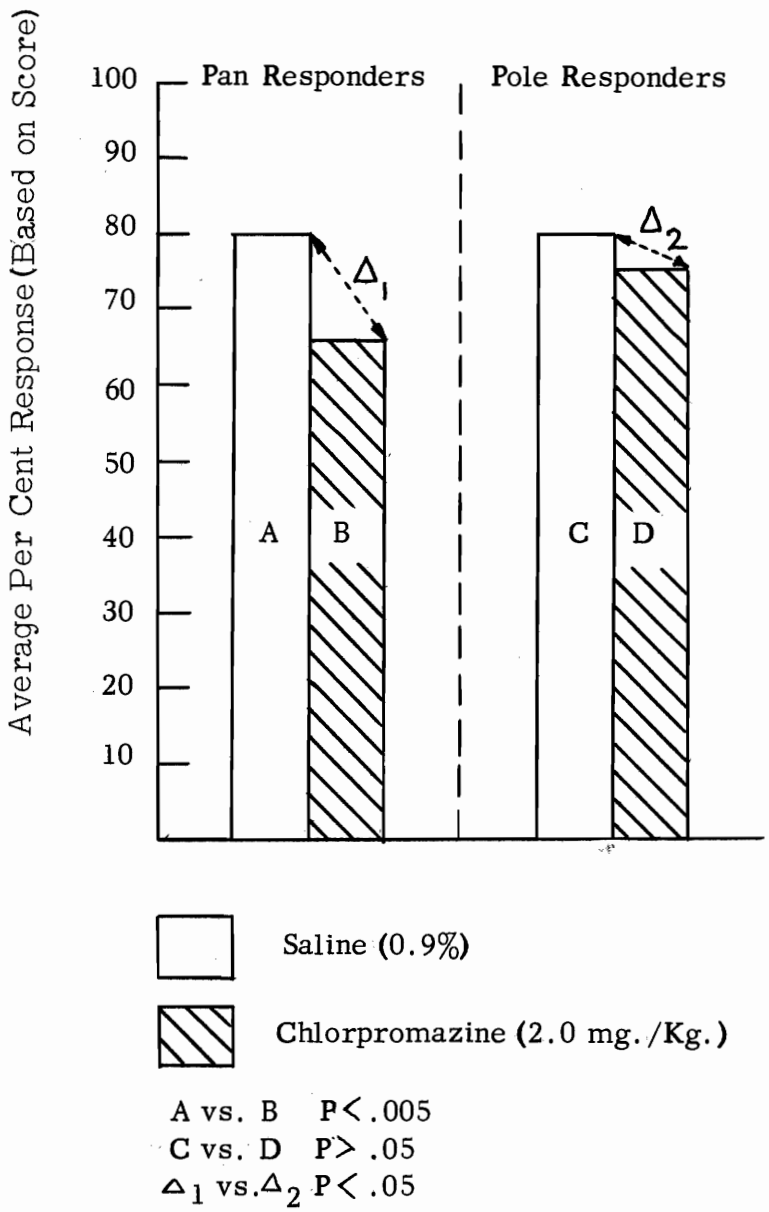


Figure 5. The effect of chlorpromazine (2.0 mg./Kg.; 1/8 TD_{50}) on conditioned avoidance responses (CR's) in Peromyscus maniculatus gracilis.

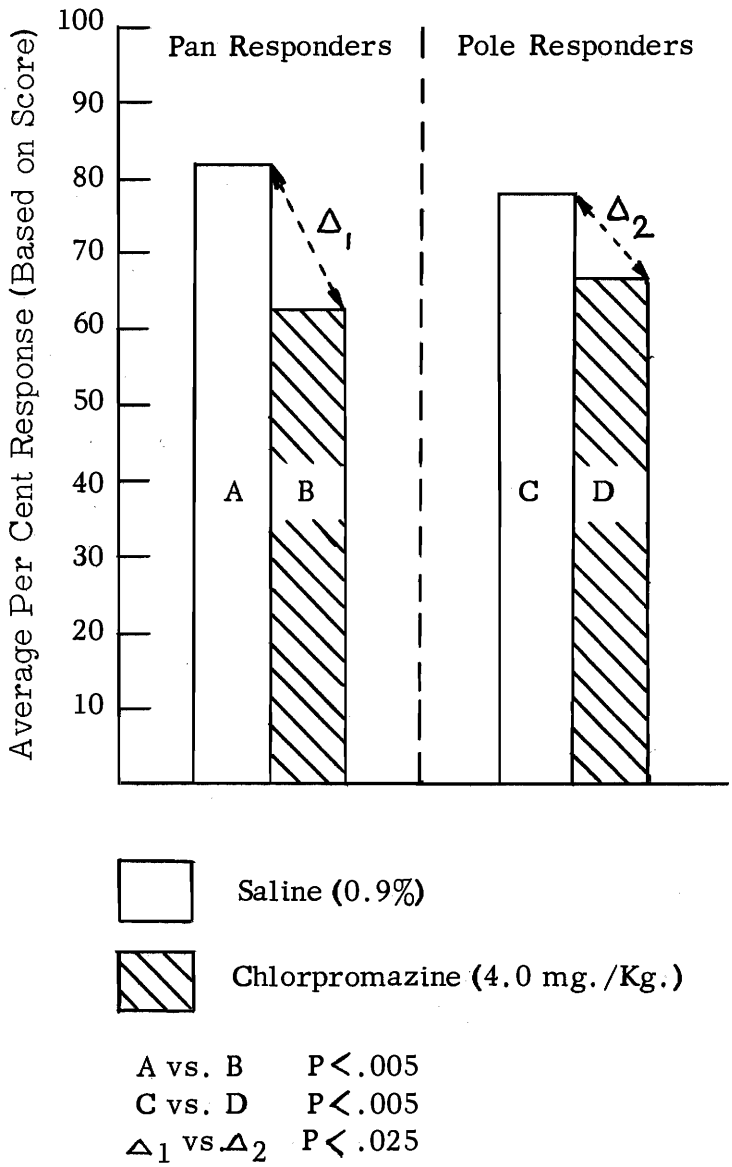


Figure 6. The effect of chlorpromazine (4.0 mg./Kg.; 1/4 TD_{50}) on conditioned avoidance responses (CR's) in Peromyscus maniculatus gracilis.

not considered to be a part of its behavioral repertory (terrestrial escape; pan response).

However, the results obtained reveal several quantitative discrepancies between these two types of conditioned avoidance behaviors. For example, at the end of an equivalent amount of training (48 trials), the total population of pole responders demonstrated a significantly higher level of conditioning than did the total population of pan responders (78% CR's vs. 56% CR's). During these training trials it was often observed that several of the animals which were being conditioned to produce a terrestrial means of escape would repeatedly leap from the escape pan back onto the electrified grid. This observation is in agreement with that reported by King and Shea (1958), and such behavior may undoubtedly contribute to the comparatively low level of conditioning in the total population of pan responders. However, a similar discrepancy in level of avoidance conditioning can also be seen when such animals are excluded from the study and an examination is made of the acquisition curves which represent only the best responders in each experimental group (selected population). In this situation the difference between the two groups was not as marked, but the pole responders still made significantly more CR's than the pan responders. Consequently, it is apparent that, in this subspecies, conditioned avoidance behavior is more readily acquired when a technique is employed which takes into consideration the innate escape pattern of the experimental animal as opposed to one which ignores genetically determined behavior and depends predominantly upon learning.

Another dissimilarity between the two conditioned avoidance behaviors was the

rate at which they underwent extinction. As shown in the results (Figure 4), the avoidance behavior of the pole responders was considerably more resistant to extinction than was that of the pan responders. Although both experimental groups started the study at the same level of conditioning (100% CR's), at its termination the pole responders were exhibiting 32% more CR's than were the pan responders. Therefore, with respect to extinction, the genetically influenced behavior is the more stable of the two conditioned avoidance behaviors investigated.

A third quantitative difference was the degree to which the behavior in each experimental group could be altered by the same dose of chlorpromazine. From the results obtained (Figures 5 and 6), it is manifest that small, non-toxic doses of chlorpromazine can significantly interfere with both types of avoidance response. It is also evident that, as the dose of chlorpromazine was increased, the drug produced a greater suppression of avoidance behavior. These results are not unexpected and agree with the many reports cited in the introduction to this section relative to the effects of chlorpromazine on conditioned avoidance behavior. It is interesting to note, however, that twice as much chlorpromazine (4 mg./Kg.) was required to depress significantly the avoidance behavior of the pole responders as was necessary to produce a similar effect on the behavior of the pan responders. Furthermore, at both the 2 mg./Kg. and 4 mg./Kg. dose levels, the magnitude of drug interference with avoidance behavior was significantly greater in pan responders than in pole responders. This provides additional evidence for the greater stability of genetically determined behavior.

In accordance with the results discussed above, it is apparent that the naturally occurring arboreal escape response of P.m. gracilis represents a behavior which can be easily replicated in the laboratory. Moreover, the avoidance behavior which results from the conditioning of such a response is more readily acquired, less readily extinguished, and less susceptible to the effects of chlorpromazine than is avoidance behavior based on the conditioning of a non-genetically determined response.

IV. THE EFFECT OF CHLORPROMAZINE ON EXPLORATORY DRIVE

A. Introduction

Many animals have a general tendency to investigate thoroughly their natural surroundings; they approach, enter, and explore all accessible areas within their specified domain. This investigative activity, commonly known as exploratory behavior, may be defined as the locomotor activity of an organism in a novel environment which offers no immediate rewards such as food or water. This type of behavior has been studied in a number of animal species including the cockroach, Blattela germanica (Darchen, 1952), the hive bee, Apis mellifera (Lindauer, 1953), the rhesus monkey, Macacca mulatta (Butler, 1953; Harlow et al., 1956), and the chimpanzee, Pan troglodytes (Welker, 1956). However, the tame Norway rat, Rattus norwegicus, is the animal whose exploratory behavior has been most extensively studied, and the following discussion is based principally on results obtained with this species. Much of the significant work in this area has been reviewed by Barnett (1958).

In contrast to experiments based on goal-directed behavior, in which the experimenter determines the "correct" response of the animal, laboratory investigations of exploratory behavior involve a non-specific response which is recorded as a function of distances traversed or areas investigated. For example, a common technique involves placing the experimental animal in an unfamiliar maze (simple or complex) whose length has been arbitrarily divided into a number of units. The animal's exploratory drive is then measured in terms of the number of units traversed and/or the

number of blind alleys entered within a specified period of time.

By means of the above technique, or variations of it, a number of workers have studied the motivational factors which influence exploratory activity. Adlerstein and Fehrer (1955) have demonstrated that food deprivation tends to increase exploratory behavior and have suggested that an elevated level of general activity is responsible for this phenomenon. On the other hand, Montgomery (1953) has shown that exploratory behavior is independent of the general activity drive, in that animals which have been deprived of activity do not differ from normal animals in the quantity of exploratory behavior exhibited. This same investigator, in collaboration with Monkman (1955), has also conducted studies which revealed that fear, induced immediately prior to a period of exploration in a novel environment, exerts no effect upon exploratory activity. Accordingly, these investigators have maintained that fear is not an incentive for exploration. A number of experiments indicate that stimulus novelty is the major motivating factor behind exploratory behavior. For example, the experiments of Berlyne (1950) show that rats spend more time exploring new things than things which they have already explored and that the second time they enter a situation they spend less time exploring it than they do on the first occasion. Montgomery (1951) also showed that the amount of exploratory behavior is inversely proportional to the duration of exposure to the novel environment and that it is directly proportional to the size of the environment.

Evidence which suggests that exploratory drive is an intrinsic component of animal behavior per se can be found in the observations of Montgomery (1954), and Myers and

Miller (1954). These workers found that in learning experiments the opportunity to explore an area can act as a reward. Furthermore, the tendency of an animal to explore thoroughly a novel environment constitutes a strong drive which persists in the face of other potent drives. This has been convincingly demonstrated by the work of Zimbardo and Montgomery (1957) in which hungry and thirsty rats were observed to explore a maze extensively before consuming any of the food and water which was available at many points within the apparatus.

All of these observations indicate that exploratory activity is a response pattern in its own right and that, in the laboratory rat, it probably results from a general tendency to behave so as to vary the stimulus situation experienced by the animal from moment to moment and to avoid what has just been experienced (Barnett, 1958). The activity, thus initiated, persists until the novelty is exhausted or until some specific need becomes overwhelmingly strong.

A considerable amount of empirical evidence supports the theory that in wild animals exploratory behavior is of definite survival value. In this respect, investigative activity often serves a dual purpose: it familiarizes the animal with the topography of its environment and provides essential information relative to future routes of escape from predators. Moreover, during exploration, the animal samples much of the edible or potable materials encountered (Barnett and Spencer, 1953) and, thus, is informed of accessible sources of food and water.

From this brief discussion, it would appear that exploratory behavior is an important part of the process by which an animal adapts itself to a particular environment.

Because such behavior is essential for the survival of the species and, therefore, is molded by the pressures of natural selection, it would not be unreasonable to assume that the initiation of exploratory behavior is controlled largely by genetic determinants. However, the quality and quantity of such behavior may be dependent upon the environmental situation imposed upon the animal. Thus, a slight alteration in the environment can markedly alter the animal's exploratory activity. For example, it is known that wild rats exhibit a great deal of exploratory activity in that they will investigate extensively all accessible areas within their domain (Barnett, 1958). However, if the environmental setting is altered by the introduction of a new object into an area already familiar to the rat, the animal avoids the object and investigative activity is reduced (Chitty and Shorten, 1946). Such avoidance of unfamiliar objects in familiar territory and the resulting decreased exploration has survival value of its own: it protects the wild rat from compulsive exploratory and sampling behavior which would ordinarily lead it into a trap or result in the ingestion of poison bait (Chitty, 1954).

The above phenomenon illustrates that the character of the exploratory behavior exhibited by an animal may be influenced markedly by the environment within which the behavior is elicited. It is also logical to assume that the exploratory behavior shown by an animal in an environment which approximates its natural habitat may be considerabl different from that expressed in this same environment by an animal which is foreign to such a habitat. However, with the exception of the studies cited above, little is known of the naturally occurring exploratory behavior of animals. Moreover, few attempts have been made to examine exploratory activity in a laboratory situation which approxi-

mates the habitat of the experimental animal. Consequently, it is not surprising that there is a paucity of information pertinent to the effect of drugs on such behavior.

In view of these observations, it was thought worthwhile to design, a priori, a laboratory apparatus which could measure, in an appropriate animal, exploratory activity characteristic of this animal in its natural habitat. It was expected that such behavior might vary quantitatively and/or qualitatively from that exhibited in the same apparatus by another animal, similar in genotype and phenotype to the animal for which the laboratory apparatus was expressly designed but differing from it in choice of natural habitat. Moreover, it was anticipated that an evaluation of the effect of chlorpromazine on the two exploratory behaviors described above might reveal marked differences in their susceptibility to the drug. Consequently, a series of experiments were designed to evaluate, by means of a complex maze, the exploratory activity of two closely related races of deermice which differ in ecology (P.m. bairdi and P.m. gracilis).

Bairdi is a true grassland subspecies and makes its nest in a ground burrow. Once these animals leave the nest, they are subject to predation, and their principal means of avoiding predators are the use of pathways under cover and flight back to the burrow or some other place of concealment. Since bairdi is an animal whose survival is dependent upon its familiarity with underground tunnels and labyrinths, it is assumed that the need to explore such areas is a genetically determined part of its behavior. On the other hand, gracilis is a woodland subspecies which often depends on arboreal

methods of avoidance, discussed in the previous section, rather than on underground pathways. Therefore, it is assumed that this animal has little genetically determined need to explore underground passages.

The maze, which was composed of a series of covered passageways and blind alleys, more closely resembled an environment which could be readily found in the natural habitat of bairdi than in that of gracilis. Thus, it was expected that, in this experimental situation, the two subspecies would exhibit marked differences in exploratory behavior, per se, as well as in the effect of chlorpromazine on such behavior. Specifically, it was hypothesized that, in this complex maze, the exploratory behavior of bairdi would be greater in amount, more systematic, and more resistant to alteration by chlorpromazine than would that of gracilis.

B. Methods

The experimental subjects consisted of 96 adult male and female mice: 48 of the subspecies Peromyscus maniculatus gracilis and an equal number of the subspecies Peromyscus maniculatus bairdi. Because of the importance of novelty as a stimulus for exploratory activity, only novice animals were employed throughout these studies. The animals were housed (8/cage) according to subspecies and sex.

The apparatus employed to evaluate exploratory behavior consisted of a complex electronic maze constructed of opaque, black Plexiglass, with over-all external dimensions of 46 in. x 20 in. x 2 in. high. The interior of the maze, as illustrated in Figure 7, comprised a transversing runway from which 6 blind alleys could be entered. The

runway and all blind alleys were 2 in. wide x 2 in. high. The total length of the runway was 112 in., whereas the length of the blind alleys varied from a minimum of 4 in. to a maximum of 6 in. Figure 7 also illustrates the means by which exploratory activity was detected. It can be observed that photoelectric cells and oppositely positioned light sources were placed near the end of all blind alleys as well as at various intervals along the runway. In all, there were 12 such light-photocell units. It should be noted that these devices were fastened to the external wall of the passageways so that the internal maze environment was not markedly altered at these points. When functioning, a constant, faint ray of light from the light source passed first through a red filter to decrease its visibility and then through a small opening in the proximal wall of the passageway. Once across the passageway, the beam passed through a similar opening in the distal wall to the photoelectric cell. Interruption of this beam activated an electrical circuit which resulted in the numerical recording of the event on an automatic counter. Each light-photocell unit was connected to a separate counter so that an accurate record of the exploratory activity of an animal was available for 12 areas within the maze. It can also be noted in Figure 7 that the maze had no floor. When operative, the maze rested on a paper-covered, foam-rubber mat placed on a flat surface. The mat served to exclude light and sound and helped to maintain a constant environment within the maze. The paper served as convenient flooring in that it could be changed after every trial to prevent the formation of scent trails which might alter exploratory behavior. In this respect, it is appropriate to mention that several times

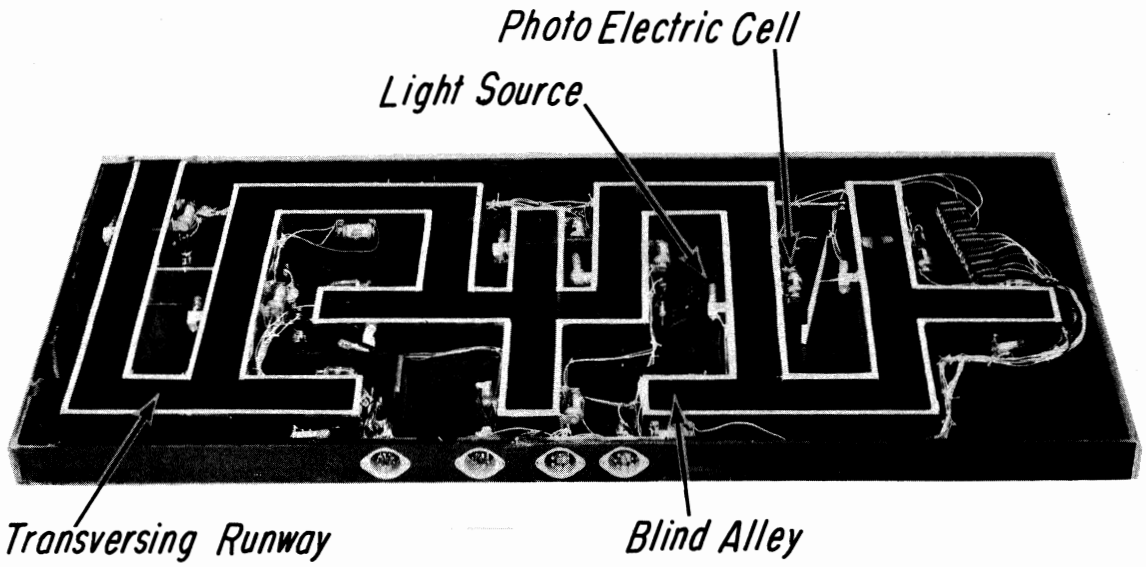


Fig.7- INTERIOR OF THE MAZE (BOTTOM VIEW)

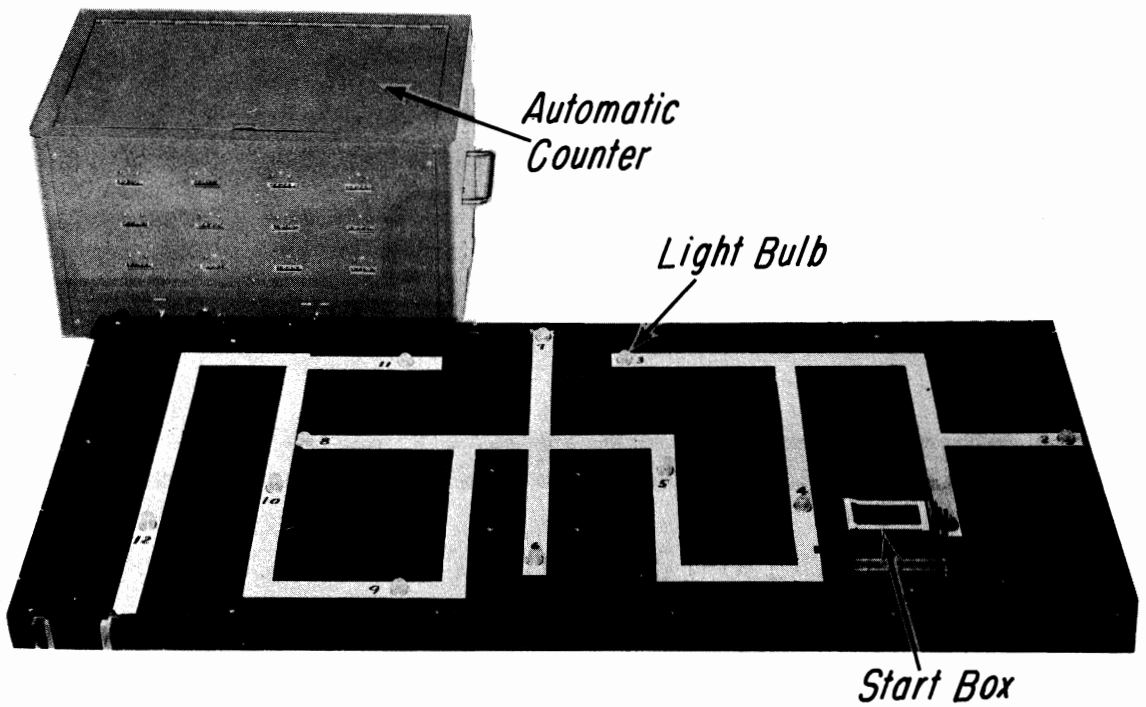


Fig.8.-OPERATIONAL VIEW OF THE MAZE

in the course of these studies, the internal walls and roof of the maze passageways were rubbed with the hides of both subspecies so as to preclude interference from scent trails.

An operational view of the maze and the panel of 12 automatic counters can be seen in Figure 8. The configuration of the maze is clearly represented by the white lines painted on the top surface of the apparatus. The 12 numbers which appear on these lines indicate the locations of the mechanisms used to detect activity. Also evident on this surface are 12 small electric bulbs, each of which is connected to a photocell in the immediate vicinity. Consequently, when the light beam to a photocell was interrupted, not only was a count for that area automatically recorded, but also the brief illumination of the bulb indicated the animal's presence in that section of the maze. Another part of the apparatus, visible in Figure 8, which warrants description is the "start box." This was fabricated of the same material as the maze and had over-all dimensions of 4 in. x 2 in. x 1 1/2 in. high. One end of the "start box" consisted of a sliding door through which the animal was introduced into the box; the floor of the "start box" was removable so that the animal gained access to the maze through a circular hole (1 3/4 in. diameter) in the roof of the runway. Once the animal had entered the maze (as shown by activation of photocell number 1), its re-entry into the "start box" was prevented by sliding the floor of the box back into its original position.

In order to contrast the exploratory behavior <u>per se</u> exhibited by the two subspecies of deermouse in this maze, each of 16 animals (8 males and 8 females) from each sub-

species was subjected to the following procedure. It was removed from its home cage and placed in the "start box" for 1 minute. At the end of this period of time, the animal was allowed access to the maze in the manner described above and was permitted to investigate the area for 1 hour; its exploratory activity was recorded for each 10-minute interval during the first 30 minutes and for each 15-minute interval thereafter. At the end of the hour, the maze was lifted, the animal was removed and returned to its home cage. At the same time each day a novice male and female of each subspecies were subjected to the above procedure in a randomized order.

Three criteria of exploratory activity were employed: latency to enter the maze, total maze activity, and blind alley maze activity. The latency to enter the maze, as measured by the amount of time that elapsed between the removal of the "start box" floor and the activation of photocell number 1, provided an indication of the eagerness of the animal to enter the environment; the total activity, as measured by the sum of the counts from all 12 photocells, provided an indication of the general level of the animal's activity in the environment; the blind alley activity, as measured by the sum of the counts from photocell numbers 2, 3, 6, 7, 8, and 11, provided an indication of the animal's systematic exploration of the environment.

An inspection of the results obtained in this study revealed the presence of a considerable amount of intra-subspecies variability which tended to obscure any real differences between the exploratory activity of the two races of deermouse. In an attempt to reduce this variability, all exploratory data (counts) were subjected to a logarithmic transformation before statistical analysis. The data were then examined

by means of a 2 x 2 factorial analysis of variance for the influence of subspecies, sex, and subspecies-sex interaction.

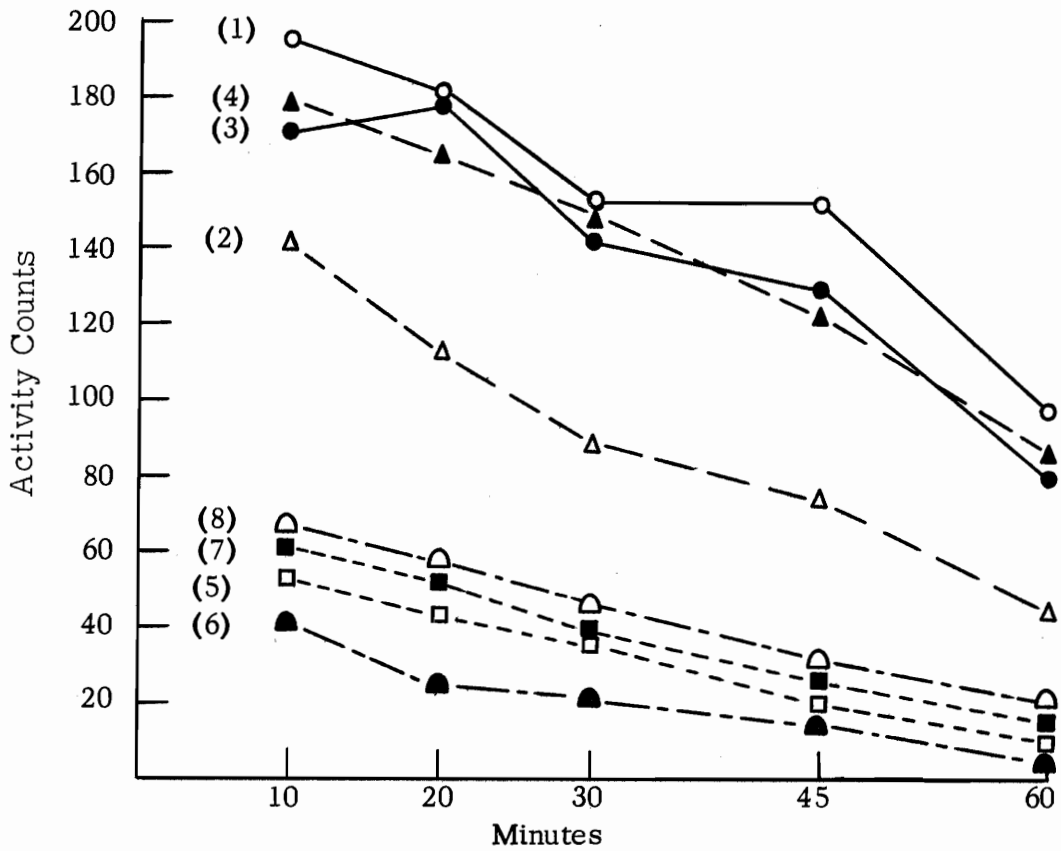
In order to evaluate the effects of chlorpromazine on exploratory activity, the following experiment was designed. Sixteen novice males from each subspecies were randomly divided into two treatment groups, arbitrarily designated as drug-treated and control animals. The drug-treated animals received 1/4 TD_{50} of chlorpromazine (4.0 mg./Kg. for gracilis and 4.6 mg./Kg. for bairdi), whereas the control animals received the requisite volume of 0.9% saline. At the previously determined time of peak drug activity, each animal was subjected to a 30-minute period of maze exploration during which time its activity was recorded for each 10-minute interval. Each day 8 such trials were conducted according to a scheme in which subspecies were alternated for every trial and treatments for every other trial, e.g., gracilis - saline, bairdi - saline, gracilis - chlorpromazine, bairdi - chlorpromazine, etc. This entire procedure was repeated using a larger dose of chlorpromazine and 16 novice females of each subspecies as the experimental animals. In this study, the drug-treated group received chlorpromazine at a dose level of 3/8 TD_{50} (6.0 mg./Kg. for gracilis and 6.8 mg./Kg. for bairdi), whereas the control animals received the requisite volume of 0.9% saline.

The same criteria of exploratory activity described previously were employed in the drug studies, with the exception that blind alley activity was expressed as a per cent of total activity in order to quantitate systematic exploration. The blind alley activity data were normalized by means of an arc sine transformation, whereas the

total activity data were subjected to a logarithmic transformation. In order to reduce intra-subspecies variability, the data obtained during the three 10-minute intervals were pooled; the pooled data were statistically analyzed by means of a 2 x 2 factorial analysis of variance for the influence of subspecies, treatment, and subspecies-treatment interaction on exploratory behavior.

C. Results

The exploratory behavior of the two subspecies as a function of time and activity can be seen in Figure 9. It is apparent that maze activity (both total and blind alley) decreases as the amount of time spent in the environment increases. For example, the total activity count for gracilis females (curve 1) was 196 for the first 10-minute interval, whereas it was only 98 for the last 15-minute interval. Similarly, blind alley activity in female mice of this subspecies (curve 5) was 54 for the first 10-minute interval, whereas it was only 12 for the last 15-minute interval. The Figure also shows that gracilis males (curves 2 and 6) exhibited a comparatively low level of exploratory activity when compared with the level of activity displayed by other animals included in this study. These animals demonstrated significantly less total and blind alley activity ($P < .05$) than did any of the other mice. A considerable amount of intra-subspecies variability precluded statistical significance for the more subtle differences observed. However, it should be noted that, although gracilis females demonstrated the greatest amount of total maze activity (curve 1), their blind alley activity (curve 5) was less than that exhibited by bairdi males (curve 8) or females (curve 7). Finally,



(1) P.m. gracilis (♀) total activity

(2) P.m. gracilis (♂) total activity

(3) P.m. bairdi (♀) total activity

(4) P.m. bairdi (♂) total activity

(5) P.m. gracilis (♀) blind alley activity

(6) P.m. gracilis (♂) blind alley activity

(7) P.m. bairdi (♀) blind alley activity

(8) P.m. bairdi (♂) blind alley activity

Figure 9. The one-hour exploratory behavior of two subspecies of Peromyscus maniculatus in a complex maze.

it can be seen from this Figure that sex has relatively little influence on the exploratory behavior of bairdi.

Although the mean latency prior to entering the maze was somewhat longer for gracilis than for bairdi and tended to be longer in males of each subspecies than females, statistical analysis of the data indicated there was no significant difference either in the latency of the two subspecies or in the latency of males and females within a subspecies. The mean latencies (in seconds) for the various groups were as follows: gracilis males, 14.3; gracilis females, 12.5; bairdi males, 11.3; bairdi females, 10.0.

The effect of chlorpromazine vs. saline on the total 30-minute exploratory behavior of the two subspecies can be seen in Figure 10. In this and in subsequent Figures, only statistically significant ($P < .05$) results are reported below the abscissa. The total exploratory behavior (general activity) exhibited by the various experimental groups after the administration of 0.9% saline was qualitatively similar to that seen during the one-hour study described above. Thus, gracilis males again showed significantly less activity ($P < .05$) than the other saline-treated animals, whereas the females of this subspecies displayed slightly more activity than did bairdi males or females. It is evident from this Figure that the administration of equi-toxic doses of chlorpromazine can educe conspicuous differences in the total maze exploration of the two subspecies. For example, a dose of chlorpromazine equal to 1/4 TD_{50} tended to increase the total maze activity of gracilis males, whereas it significantly decreased this activity in bairdi males ($P < .02$). At a higher dose level (3/8 TD_{50}), chlorpromazine produced

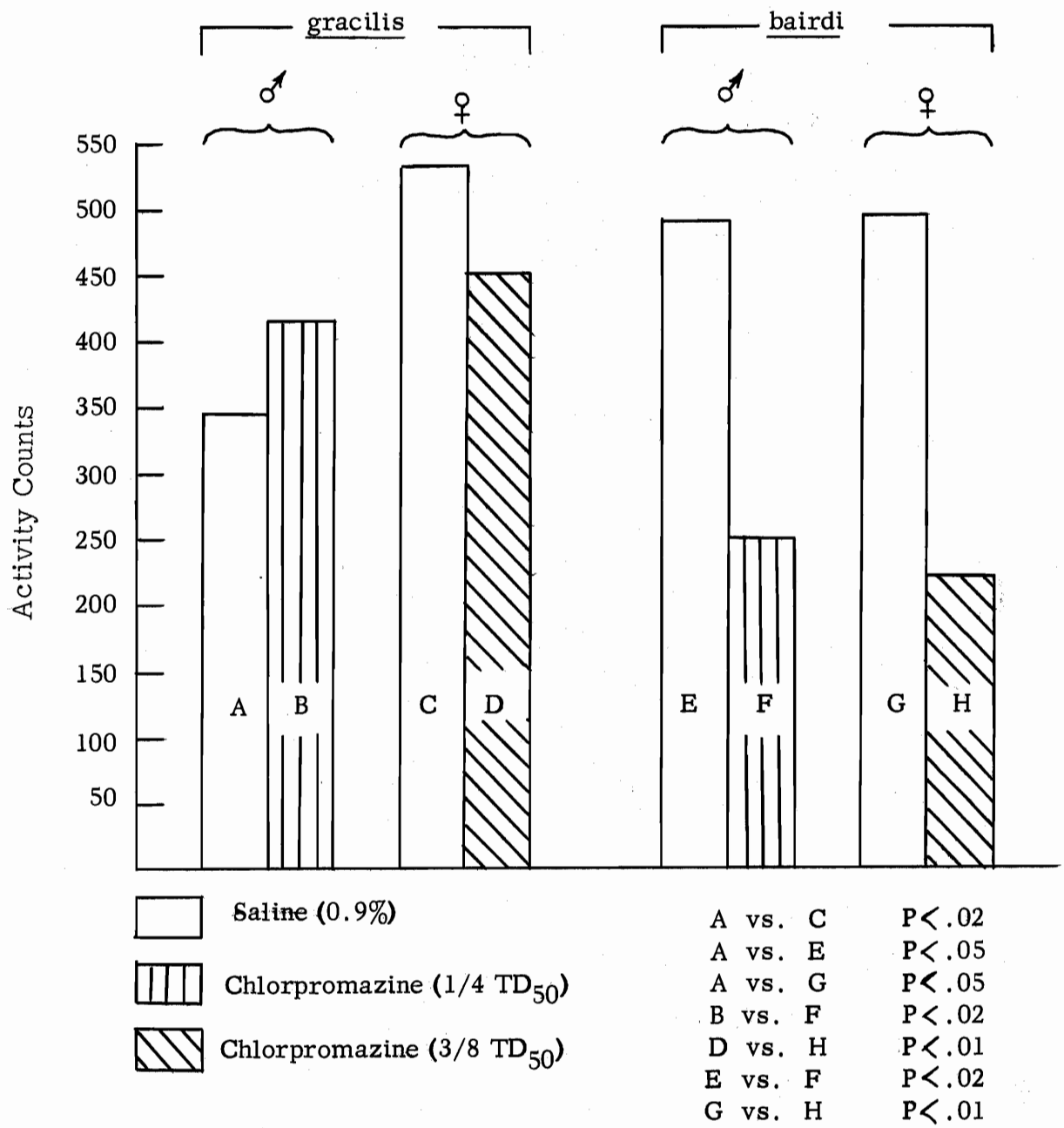


Figure 10. The effect of chlorpromazine on the total 30-minute exploratory behavior of two subspecies of Peromyscus maniculatus in a complex maze.

only a slight reduction in the activity of gracilis females, whereas this amount of drug produced a highly significant reduction ($P < .01$) in the activity of bairdi females.

The effect of chlorpromazine vs. saline on the blind alley 30-minute exploratory behavior of the two subspecies is illustrated in Figure 11. To correct for the differences in the general activity observed in various groups, the blind alley activity shown in this Figure is expressed as a per cent of total maze activity. Here it can be seen that the sex of the experimental animal had only a negligible effect on blind alley exploratory behavior. It is apparent that saline-treated bairdi exhibited a greater amount of blind alley activity than did saline-treated gracilis. This difference was significant with respect to males ($P < .05$) but not significant with respect to females. It is also evident from the Figure that equi-toxic doses of chlorpromazine can bring about conspicuous differences in the relative amount of blind alley exploratory activity displayed by the two subspecies. For example, a dose of 1/4 TD_{50} had essentially no effect on this type of activity in gracilis males, whereas this amount of chlorpromazine tended to increase the blind alley activity of bairdi males. The difference between the two drug-treated subspecies was highly significant ($P < .01$). Moreover, similar results were observed at a higher dose level of chlorpromazine (3/8 TD_{50}). This dose of drug tended to decrease the blind alley activity of gracilis females, whereas it significantly increased ($P < .05$) the relative amount of such activity exhibited by bairdi females. Again, the difference between the two drug-treated subspecies was highly significant ($P < .01$).

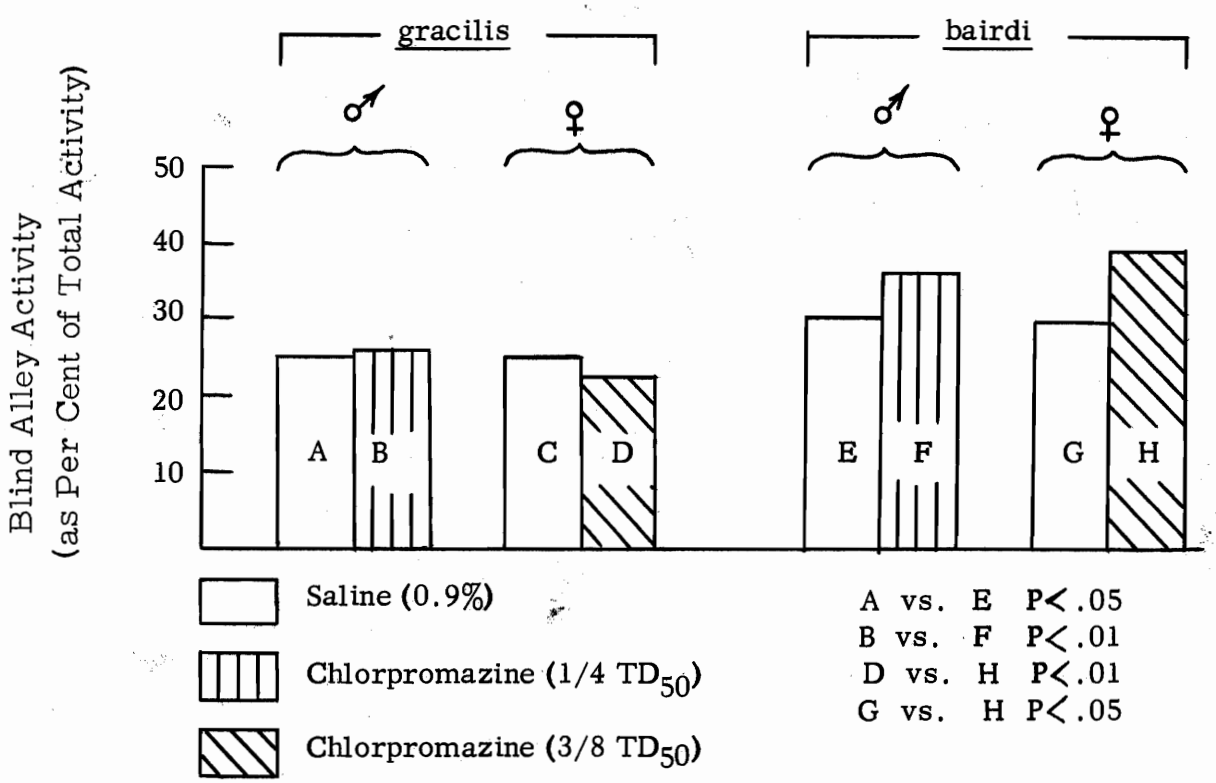


Figure 11. The effect of chlorpromazine on the blind alley 30-minute exploratory behavior of two subspecies of Peromyscus maniculatus in a complex maze.

The effect of chlorpromazine on "start box" latency exhibited by the two subspecies of deermouse can be seen in Figure 12. The latencies of the saline-treated animals are not significantly different from one another and agree with those already reported for the one-hour study. It is also interesting to note that again equi-toxic doses of chlorpromazine produced discrepant effects on the two subspecies. For example, at both dose levels, chlorpromazine had no significant effect on the latency of gracilis to enter the maze, yet equivalent doses of drug significantly increased the latency of bairdi to enter the maze ($P < .01$).

To summarize the results of these studies, it may be said that the two saline-treated subspecies exhibited similar propensities to enter the maze and, with the exception of gracilis males, similar amounts of total maze exploration. The two saline-treated subspecies differed in blind alley exploration in that bairdi expended a larger proportion of its total activity investigating blind alleys than did gracilis. However, the greatest inconsistencies between the behavior of the two subspecies were seen when these animals were under the influence of equi-toxic doses of chlorpromazine. Here it was observed that the exploratory behavior of bairdi, with the exception of its blind alley activity, was markedly reduced by the drug, whereas the exploratory behavior of gracilis was seemingly resistant to any modification by chlorpromazine.

D. Discussion

The results clearly indicate that these two closely related subspecies of deermouse differ in their pattern of exploratory behavior in a complex maze. Although all animals

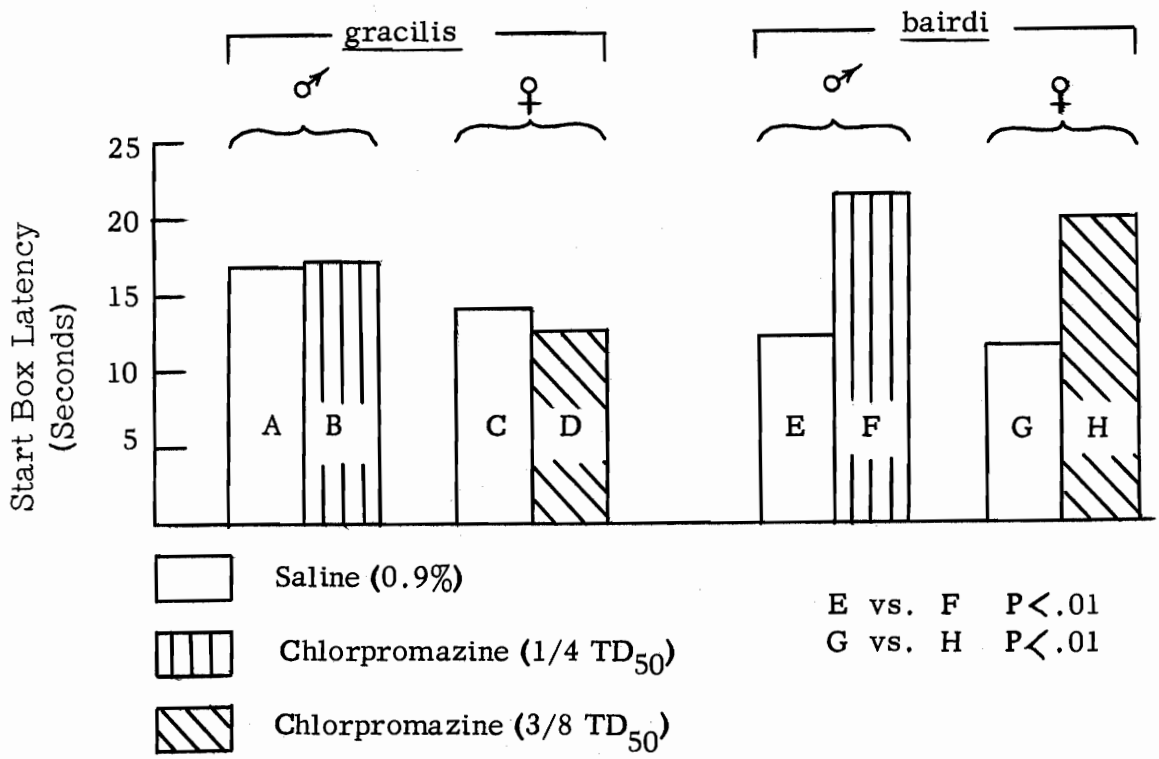


Figure 12. The effect of chlorpromazine on the start box latency exhibited by two subspecies of Peromyscus maniculatus.

(with the exception of gracilis males) exhibited a similar amount of total maze activity (Figure 10), it is evident that bairdi demonstrated a greater inclination to explore all blind alleys than did gracilis (Figure 11). This would imply that in this maze the exploratory behavior of bairdi is more systematic than that of gracilis.

In order to account for the above, it is assumed that this systematic pattern of exploratory activity is genetically determined in bairdi in that survival of this subspecies is often dependent upon thorough familiarity with naturally occurring terrestrial maze systems. As a corollary, it may be inferred that gracilis has had little ecological opportunity to come into contact with such maze systems and, consequently, probably lacks genetic mechanisms for systematically exploring such environments. Moreover, since this subspecies has had little natural experience with terrestrial mazes, the novelty of such a situation should be greater in gracilis than in bairdi. Since novelty provides a strong motivation for exploration (Berlyne, 1950; Montgomery, 1951), the maze exploratory behavior of gracilis is characterized by a considerable amount of activity. However, as mentioned previously, this animal probably does not possess the genetically determined need to explore thoroughly all blind alleys. Therefore, its maze activity lacks to a considerable degree the systematic exploration observed in bairdi.

It is also evident from the results (Figures 9 and 10) that, in gracilis, sex is an important factor in the amount of exploratory activity displayed; males are significantly less active in the maze than are females. The import of this finding is not clear and

no attempt will be made to draw any conclusions from these data. However, it should be noted that the discrepancy between males and females of this subspecies is quantitative rather than qualitative in nature. For example, it can be seen (Figure 11) that, since both male and female gracilis expend a similar proportion of their total activity investigating blind alleys, their patterns of maze exploration may be considered analogous. Furthermore, there is no significant difference in their latencies to enter the maze (Figure 12). In view of the above, both males and females were used to evaluate the effects of chlorpromazine on exploratory behavior.

The results pertinent to the effects of equi-toxic doses of chlorpromazine (Figures 10, 11, and 12) provide further evidence of the marked dissimilarity in maze exploration exhibited by the two subspecies of deermouse. For example, it is manifest that, at both dose levels, chlorpromazine had a negligible effect on the amount of both total maze and blind alley exploration exhibited by gracilis. Also, the drug did not alter significantly this animal's latency to enter the maze. This seeming resistance to the effects of chlorpromazine may be a result of the behavioral situation in which the animal was placed. It should be recalled that the exploratory behavior of gracilis in this maze was probably motivated by a strong curiosity drive. Thus, it does not seem unlikely that the large amount of novelty induced by the environment may account for the ineffectiveness of chlorpromazine in the doses employed.

On the other hand, it is obvious that, although chlorpromazine (at both dose levels) significantly decreased the amount of total maze activity exhibited by bairdi, it had little

effect on this animal's systematic exploration of the maze. Thus, the effect was predominantly on activity in transversing runways and resulted in the recording of an increase in the amount of blind alley exploration expressed as a per cent of total activity. Furthermore, in this subspecies, the drug significantly increased "start box" latency and, hence, retarded the commencement of maze exploration.

These results may be interpreted as follows: chlorpromazine had little effect on the systematic exploration of blind alleys because in bairdi such exploratory behavior is probably genetically determined and, hence, quite resistant to alteration. On the other hand, the marked influence of chlorpromazine on both the eagerness of bairdi to enter the maze and the quantity of activity which was exhibited in the transversing runways may be related to a lesser amount (than gracilis) of novelty afforded this subspecies by the maze environment.

In order to exclude the possibility that the variance observed between the two subspecies following the administration of chlorpromazine may have been due to a selective effect of the drug on a particular type of spontaneous motor activity per se, a pilot experiment was designed to evaluate the effect of chlorpromazine (3/8 TD_{50}) vs. saline on both horizontal and vertical spontaneous motor activity in 20 gracilis and 20 bairdi females. Only females were employed because it had been previously demonstrated that the females of both subspecies exhibited similar amounts of total maze activity, whereas, as discussed heretofore, gracilis males exhibited less maze activity than any of the other animals.

Spontaneous motor activity was measured in a covered plastic cage (11 in. x 7 in. x 5 in. high) by means of two photoelectric cell devices which were connected to automatic counters. For the determination of horizontal activity, a light ray was directed across the cage to an oppositely positioned photoelectric cell. This produced a beam of light (5 1/2 in. from one end of the cage and 1 in. above the floor) which was readily broken by an animal roaming on the floor of the cage. For the determination of vertical activity, a similar light ray and photoelectric cell were used. However, these were positioned so that the beam of light passed over the center of a circular platform (3 in. diameter, 2 in. high) situated at one end of the cage. Thus, this beam was located approximately 2 1/2 in. above the floor of the cage and was broken whenever an animal jumped onto the platform. The measure of spontaneous motor activity in both situations (horizontal and vertical) was the number of counts recorded (light beams interrupted) during a 15-minute trial. Each animal was subjected to a single trial, 60 minutes after the administration of either chlorpromazine (3/8 TD_{50}) or saline. The treatments were administered in a random sequence such that, at the end of the experiment, 10 animals from each subspecies had received chlorpromazine and a like number had received saline.

The results of this study were characterized by much intra-subspecies variability which tended to obscure any significant differences between the amounts of spontaneous horizontal vs. vertical activity per se displayed by the two subspecies. Nevertheless, gracilis tended to exhibit somewhat more vertical activity (42%; expressed as a per

cent of total activity) than bairdi (34%). Also, it was evident from this study that the amount of chlorpromazine employed produced only non-significant effects on both vertical and horizontal activity, which were similar for the two subspecies. For example, this dose of chlorpromazine brought about a reduction in horizontal and vertical activity which, in gracilis, amounted to 3.9% and 11.2%, respectively, whereas in bairdi, the respective reduction amounted to 2.8% and 13.1%. Therefore, it is obvious that the discrepant effect of chlorpromazine on the maze activity of the two subspecies cannot be due to a preferential depression of spontaneous motor activity. However, it is possible that the procedures employed in this experiment were not sufficiently sensitive to detect true differences in activity between the subspecies.

Nevertheless, it appears from the results discussed that small, non-toxic doses of chlorpromazine do not interfere with maze exploratory activity when such behavior is motivated either by a large amount of novelty, as in the case of gracilis, or by genetic determinants, as in the case of bairdi.

V. THE EFFECT OF CHLORPROMAZINE ON AGGRESSIVE AND AVOIDANCE BEHAVIOR

A. Introduction

Aggression is the act of initiating an attack and often is evidenced by some type of fighting behavior. This response has been induced and studied in laboratory animals by a variety of experimental methods. These methods, recently reviewed by Tedeschi et al. (1959), include the use of surgical ablation (Bard, 1928), drugs such as morphine (Sturtevant and Drill, 1957), electrical stimulation through either implanted electrodes in the central nervous system (Ranson, 1937) or footshock (Miller, 1948), and prolonged periods of isolation (Yen et al., 1958).

The influence of drugs on such behavior has been the subject of a number of investigations. It has been demonstrated that androgens tend to increase aggression in male animals (Beeman, 1947), whereas estrogens have been shown either to decrease male aggression (Clark and Birch, 1945, 1946) or to be ineffective in this respect (Gustafson and Winokur, 1960). Considerably less evidence is available concerning the effect of hormones on female aggression, probably because this behavior is more difficult to elicit. Clark and Birch (1946) have observed some increased aggression between a pair of castrated female chimpanzees following an injection of estrogen, but King and Tollman (1956) have observed that neither intact nor castrated female mice could be stimulated to fight by the injection of androgens. Recently, experimental efforts have been directed toward the effects of psychopharmacologic drugs on fighting behavior. Yen et al. (1959) have demonstrated that the chronic administration of relatively large

doses of various ataractics can suppress aggressive behavior induced in male mice by prolonged periods (3 weeks) of isolation. These same investigators imply that this may be a selective effect of these drugs in that the chronic administration of a comparably large dose of sodium phenobarbital did not alter aggressive behavior. However, Tedeschi et al. (1959) produced fighting episodes in male mice by exposing the animals to a mild footshock and by this procedure demonstrated that chlorpromazine, prochlorperazine, and phenobarbital suppressed fighting episodes only in doses which produced a moderate or marked degree of motor inactivation. These results have since been confirmed by Janssen et al. (1960) in an experiment in which aggressive behavior was induced in male mice by subjecting them to 24 hours of isolation.

Although fighting responses were elicited in all of the ataractic studies cited above, the techniques employed produced aggressive behaviors which were limited in quality as well as in quantity. For example, in most instances, the fighting episodes were characterized by bouts of sparring and nipping between mice. These are components of mild rather than severe aggression. Moreover, the number of mice which would exhibit fighting episodes when subjected to such techniques varied from a mimimum of 10% (Janssen et al., 1960) to a maximum of 67% (Yen et al., 1959). Perhaps one of the major reasons for the relative inefficacy of the above methods is the choice of experimental animal. In most of the aforementioned investigations, aggressive behavior was studied in animals which, for many generations, have been genetically selected for docility and, hence, possess little innate aggressiveness. For example, albino mice

such as the CF #1 and Swiss strains have commonly been used in aggression studies even though Allee (1942) has demonstrated that black mice are much more aggressive and fight harder than either brown mice or the placid white mice. A similar observation was made by Scott (1942) who, in a study involving the genetic differences in social behavior of inbred strains of mice, reported that C57 strain black mice were wilder and more active than C (Baqq) albinos. These observations indicate that fighting behavior might best be studied in an animal which possesses more innate aggressiveness than that which occurs in the experimental animals presently employed for the evaluation of such behavior.

One group of animals which should possess a considerable amount of innate aggressiveness is that categorized as predators. Since aggression is an integral part of predacious behavior and because such behavior is essential for the survival of the organism and propagation of the species, it is not illogical to assume that in predatory animals aggressive behavior may be largely genetically determined. Although a limited number of investigations have been made pertinent to aggression per se in predatory animals, e.g., Murie's study of the behavior of wolves (1944), there is a lack of information relative to the effects of drugs on such behavior.

In view of these observations, it was thought worthwhile to examine the aggressive behavior of a small predatory rodent, Onychomys leucogaster. It was felt that useful information might be acquired if a comparison were made between the effect of chlorpromazine on the innate aggressive behavior of this species and the effect of the drug

on a behavior of the animal which was more dependent upon learned determinants. Consequently, a series of experiments were designed to compare the behavior of Onychomys leucogaster in a situation which required the animal to perform an aggressive act in order to forestall a noxious stimulus with this animal's behavior in a situation which required it to run to a "safe area" in order to forestall a noxious stimulus. Specifically, the two behaviors were compared for acquisition of the response, extinction of the response, and acute effect of chlorpromazine on the response. It was hypothesized that the aggressive behavior of this animal would be more readily acquired, less readily extinguished, and more resistant to modification by chlorpromazine than would its "safe area" avoidance behavior.

B. Methods

The experimental subjects were 12 mice (7 male and 5 female) of the species Onychomys leucogaster. The animals were all adults and were housed individually. At the onset of the study, the animals were randomly divided into two experimental groups of 6 animals each; one group was arbitrarily designated as avoidance animals and the other group as aggressive animals.

The apparatus employed to evaluate the avoidance response consisted of a shuttle box with a starting section at one end and a "safe area" pan close to the opposite end. This was the same device as that used to appraise the terrestrial (pan) response in P.m. gracilis and has been described in detail previously (see page 27). The above apparatus, when modified as described below was also used to evaluate aggressive

behavior. In this situation, the pan area was blocked off by a partition which divided the shuttle box approximately in half and served to form an area 10 1/2 in. x 4 in. x 8 in. high. It was in this chamber that the aggressive behavior was elicited and examined.

The mice were trained to respond to a buzzer (CS) and avoid a shock (US), either by finding and remaining on the "safe area" pan for a period of 5 seconds (avoidance animals) or by continuously attacking, for a period of 5 seconds, a small victim mouse (CF #1; 14 - 17 g.) which had been placed in the test chamber (aggressive animals). In both response situations, the following scheme was employed: a mouse was placed in the starting area and a GraLab electric timer was started. At the end of 10 seconds, the door separating the starting area from the rest of the shuttle box was removed, and the mouse was given 5 seconds exposure to the environment. Following this, the buzzer was activated for 15 seconds. If an appropriate response (attack or escape to pan) was not made within this interval, the buzzer remained on and an electric shock (60-cycle alternating current; 25 volts, delivered through a grid scrambler) was applied to the feet of the animal through the grid floor. The buzzer and shock were continued until the animal made the appropriate response or until a total period of 50 seconds had elapsed; whereupon the buzzer and shock were terminated and the animal was removed from the test environment. Each 50-second (maximum) sequence (10 seconds starting area, 5 seconds environment, 15 seconds buzzer, and up to 20 seconds buzzer and shock) constituted one training trial. Each animal received 8 such trials per day at the rate of

4 trials per 5 minutes.

It was observed during these training trials that the fighting elicited in the aggressive animals by the above procedure was so severe that the victim mouse would invariably be killed in a short time if the attacks were not interrupted. Therefore, once a positive aggressive response (5 seconds of attack) had been obtained, the fighting episode was terminated by immediately removing the aggressive animal from the test environment. However, on the last (8th) trial of each day, the aggressive animal was allowed to kill the victim mouse.

To determine the rate of acquisition of the two behaviors, both experimental groups were subjected to 48 training trials (8 per day for 6 days). If an animal failed to make at least 6 consecutive appropriate responses to either environment, CS, or US within 32 trials, training was discontinued. It was necessary to replace one aggressive animal during the course of the study for failure to meet this criterion. This animal subsequently died and was shown to have broken one upper incisor; this undoubtedly impaired its aggressive behavior.

The total number of CR's which occurred during the 48 training trials was recorded for every animal in each experimental group, and the accumulated data were examined for differences which might exist between the two groups. The results obtained in this study were subjected to statistical analysis by means of a group comparison "t" test.

To determine the rate of extinction of the two behaviors, both experimental groups

were first trained to a level of at least 6 consecutive CR's in 8 trials. Subsequently, the animals were subjected to 48 trials in which the same procedure as that employed during training was used except that the US was eliminated. The animals were given 6 days of extinction trials in blocks of 8 trials per day and the number of failures to respond to the CS was recorded. In order to determine whether true differences existed between the two experimental groups, the results were statistically analyzed by means of a group comparison "t" test.

To examine the acute effects of chlorpromazine on the two responses, the animals in both experimental groups were retrained to a level of 6 consecutive CR's in 8 trials. Because many of the animals demonstrated an appropriate response before the presentation of the CS, a scoring system, which took advantage of differential levels of conditioning, was employed to evaluate each animal's behavior. Thus, in assessing the effects of chlorpromazine, the response of each mouse was graded and recorded as follows: a mouse exhibiting an SCR (response to 5 seconds of environment) was assigned 4 points; one exhibiting a CR (response to 5 seconds of environment and 15 seconds of buzzer) was assigned 3 points; one exhibiting a UR (response to 5 seconds of environment, 15 seconds of buzzer, and up to 20 seconds of shock associated with buzzer) was assigned 2 points; and non-responders were assigned 1 point.

For the determination of drug effects, the two experimental groups (6 avoidance animals and 6 aggressive animals) were each randomly divided into two treatment groups: 3 chlorpromazine-treated animals and 3 saline-treated animals (controls). Each drug-

treated group was given 2.1 mg./Kg. (1/6 TD_{50}) of chlorpromazine and each control group was given the requisite volume of 0.9% saline. At the time of peak drug activity, all mice were subjected to 8 trials, the response noted, and the total points recorded. A cross-over design, identical to that previously described in relation to the effect of chlorpromazine on arboreal vs. terrestrial means of avoidance in P.m. gracilis (see page 32) was employed. This entire experimental procedure was repeated using doses of 4.3 mg./Kg. (1/3 TD_{50}) and 6.4 mg./Kg. (1/2 TD_{50}) of chlorpromazine in the drug-treated groups and the requisite volume of 0.9% saline in the control groups.

The data concerned with the behavioral effect of chlorpromazine vs. saline were statistically analyzed by the Wilcoxon Matched-Pairs Signed-Ranks Test (Siegal, 1956), whereas the data comparing the differential effects of chlorpromazine on avoidance and aggressive behavior were statistically analyzed by the Mann-Whitney U Test (Siegal, 1956).

C. Results

The acquisition of the two behaviors, as a function of time and trials may be seen in Figure 13. As illustrated in the Figure, the avoidance response tended to be acquired more rapidly than did the aggressive response. However, the discrepancy between the two curves probably was due to chance in that statistical analysis revealed no significant differences between the acquisition of the two responses ($P > .05$). It can also be seen from this Figure that adequate response levels were obtained in both experimental groups with a relatively small amount of training. Thus, after 48 conditioning trials,

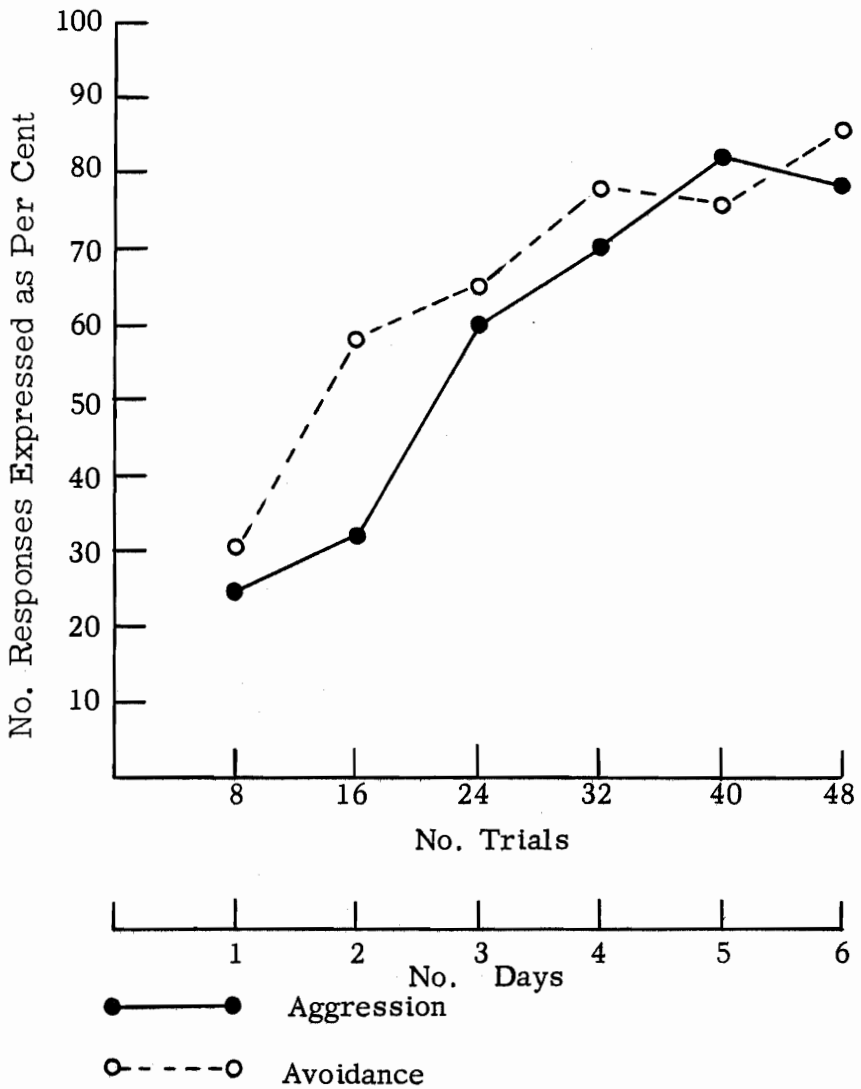


Figure 13. The acquisition of conditioned avoidance and aggression in Onychomys leucogaster.

the aggressive and avoidance animals exhibited the appropriate response to the CS 78% and 86% of the time, respectively.

The results pertinent to the extinction of the two behaviors, as a function of time and trials, are illustrated in Figure 14. Here it can be seen that the aggressive behavior was very stable and underwent essentially no extinction within the time period of this study, whereas the avoidance behavior was rapidly extinguished. Thus, at the end of 48 extinction trials, the aggressive and avoidance animals exhibited the appropriate responses to the CS 84% and 32% of the time, respectively. This difference in rate of extinction between the two experimental groups was highly significant ($P < .01$).

The effect of various doses of chlorpromazine on the two behaviors can be seen in Figures 15, 16, and 17. It can be seen in Figure 15 that 2.1 mg./Kg. (1/6 TD_{50}) of chlorpromazine significantly depressed avoidance behavior (saline vs. chlorpromazine; $P < .025$), but had no significant effect on aggressive behavior (saline vs. chlorpromazine; $P > .05$). It is obvious from this Figure that the extent to which this dose of chlorpromazine depressed avoidance behavior was significantly greater than that in aggressive behavior (Δ_1 vs. Δ_2; $P = .002$). Similar results, illustrated in Figure 16, were obtained when the dose of chlorpromazine was increased to 4.3 mg./Kg. (1/3 TD_{50}). Again, chlorpromazine significantly depressed avoidance behavior (saline vs. chlorpromazine; $P < .01$), but had no significant effect on aggressive behavior (saline vs. chlorpromazine; $P > .05$). Also, as with the lower dose, this amount of chlorpromazine had a significantly greater effect on avoidance behavior than it did on aggressive be-

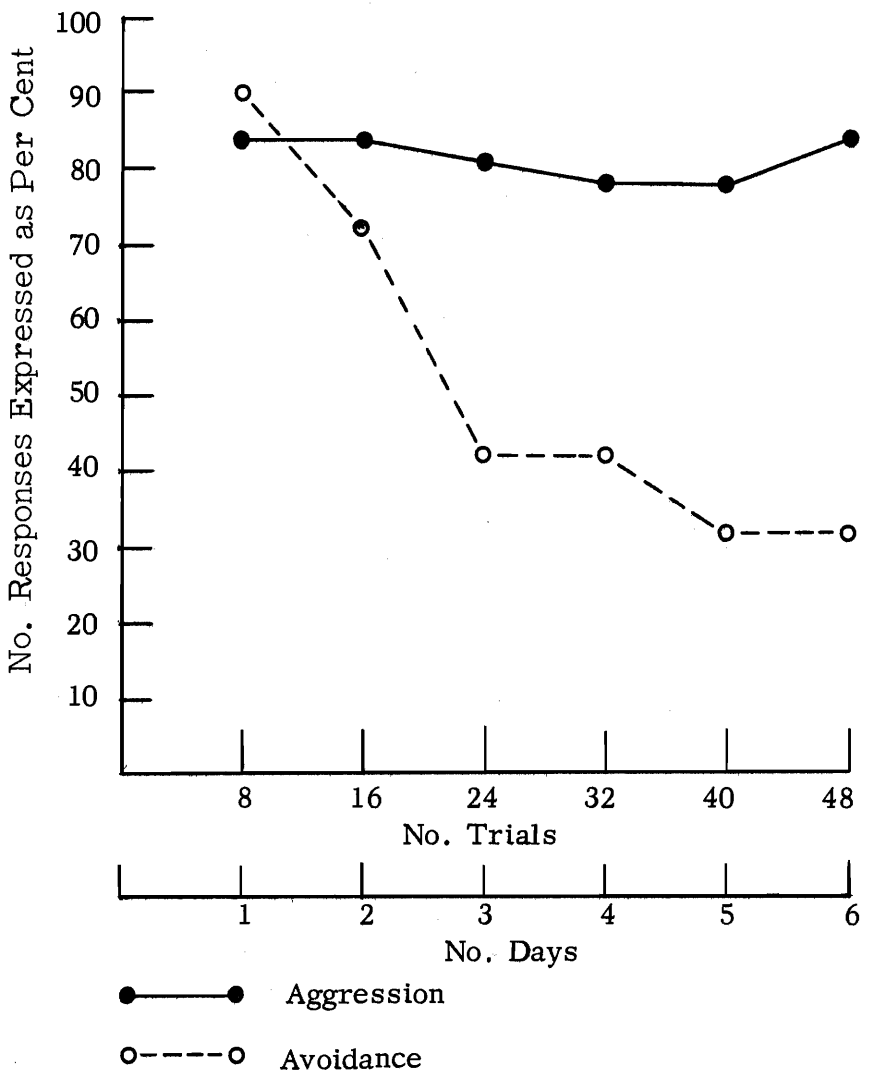


Figure 14. The extinction of conditioned avoidance and aggression in Onychomys leucogaster.

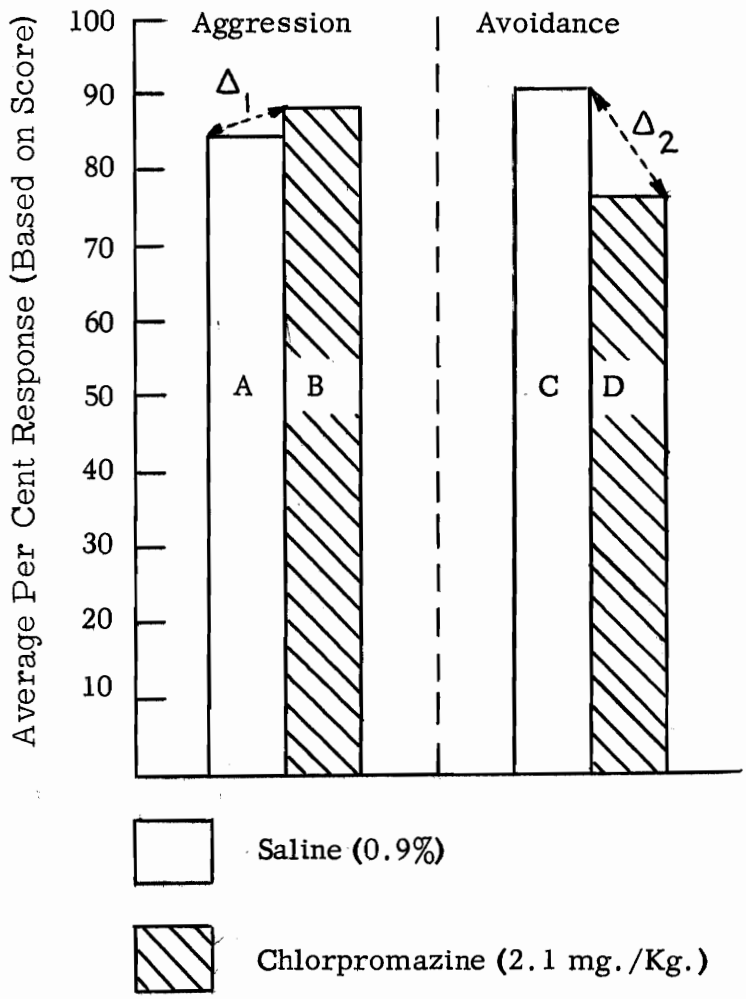
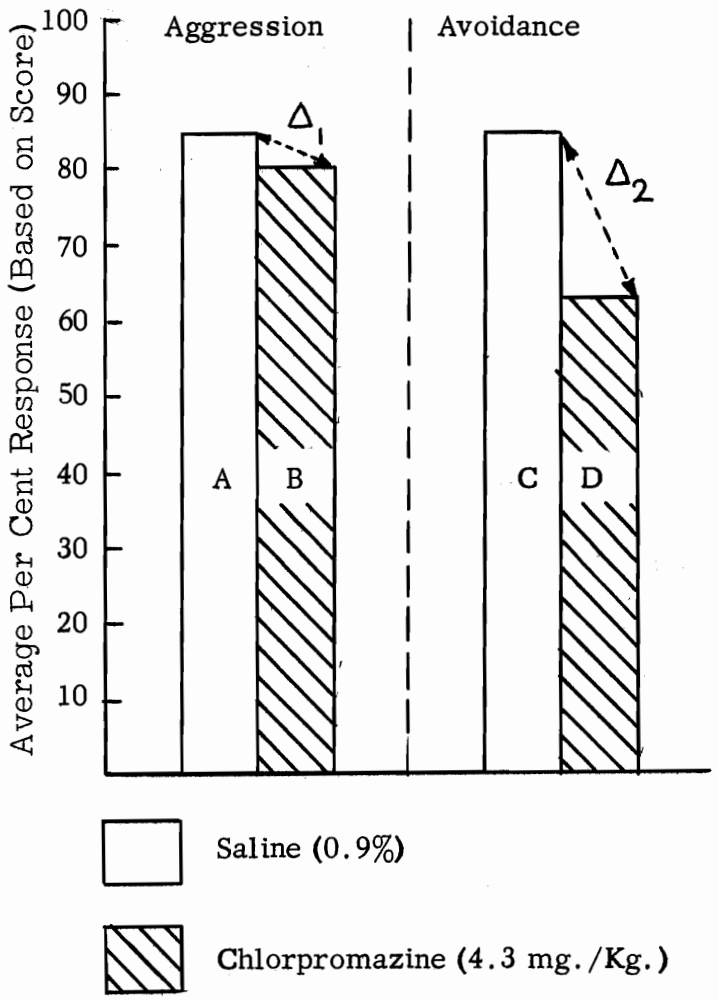
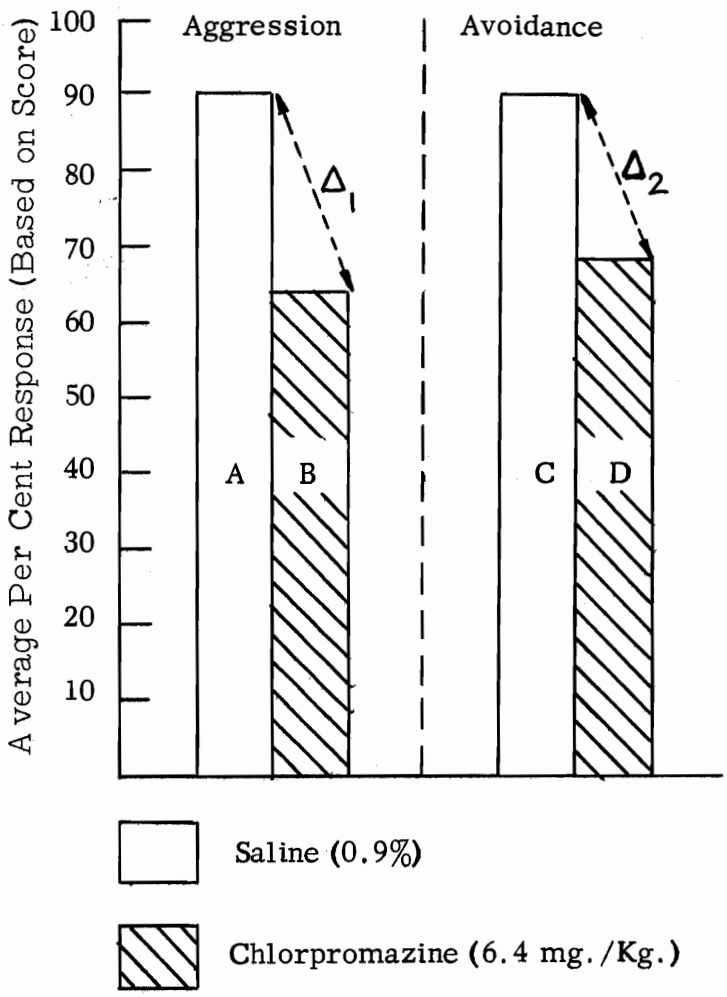


Figure 15. The effect of chlorpromazine (2.1 mg./Kg.; 1/6 TD_{50}) on aggressive and avoidance behavior in Onychomys leucogaster.



A vs. B $P > .05$
C vs. D $P < .01$
Δ_1 vs. Δ_2 $P = .015$

Figure 16. The effect of chlorpromazine (4.3 mg./Kg.; 1/3 TD_{50}) on aggressive and avoidance behavior in Onychomys leucogaster.



A vs. B $P < .01$
C vs. D $P < .01$
Δ_1 vs. Δ_2 $P > .05$

Figure 17. The effect of chlorpromazine (6.4 mg./Kg.; 1/2 TD_{50}) on aggressive and avoidance behavior in Onychomys leucogaster.

havior (Δ_1 vs. Δ_2; P = .015). When the dose of chlorpromazine was increased to 6.4 mg./Kg. (1/2 TD_{50}), the results illustrated in Figure 17 were obtained. Here it can be seen that both aggressive and avoidance behavior were significantly depressed by this quantity of drug (saline vs. chlorpromazine; $P < .01$ in both response situations). At this dose level, there was no significant difference in the magnitude of the drug's interference with the two behaviors under study (Δ_1 vs. Δ_2; $P > .05$).

Although the number of male and female animals employed was too small to permit an adequate statistical evaluation of the influence of sex, careful observation revealed that the sex of the experimental animal had little bearing on its behavior in either of the response situations (aggression or avoidance).

D. Discussion

From the results presented, it is evident that the only study in which striking differences were not noted between the two behaviors under investigation was that concerned with the rate of acquisition of the responses. Originally, it had been hypothesized that aggressive behavior in Onychomys leucogaster, because of its innate components, should be more readily acquired than a conditioned avoidance behavior. However, the results illustrated in Figure 13 do not confirm this hypothesis. An examination of the response which was required for each of the experimental groups provides a plausible explanation for the above. It should be recalled that for avoidance animals, an appropriate response to the CS consisted of finding and remaining on a "safe area" pan for

a period of 5 seconds, whereas the appropriate response for aggressive animals consisted of a continuous attack on a victim mouse for a period of 5 seconds. As evidenced by the results, the avoidance animals had little difficulty in acquiring the response. What is not evident from the results portrayed is that after a relatively few trials (8 or less), most of the aggressive animals exhibited attack behavior upon presentation of the CS. Because these attacks on the victim mouse consisted of brief episodes of mild aggression (sparring and nipping) which seldom lasted the required 5 seconds, few positive responses to the CS were recorded. Presentation of the US invariably elicited severe aggression (killing attempts) which persisted until the attack was interrupted by the experimenter or the victim mouse was killed. After several days of training, however, the initial mild aggression was virtually eliminated from the attack pattern, and many animals exhibited severe aggression upon or before presentation of the CS. Undoubtedly, the rate of acquisition of the aggressive behavior would have been substantially increased if mild rather than severe aggression had been selected as the appropriate response to the CS.

Most of the remaining results draw attention to some marked dissimilarities between the two types of behavior investigated. For example, it is evident from the results illustrated in Figure 14 that the aggressive behavior was significantly more resistant to extinction than was the avoidance behavior. In fact, at the end of this experiment, the aggressive animals responded to the CS just as frequently as they did at the start of the experiment, whereas the avoidance animals exhibited 58% less CR's than they

did initially. Thus, it appears that once severe aggressive behavior has been experimentally educed in Onychomys leucogaster, this innate response pattern becomes very stable and is quite difficult to extinguish.

A major discrepancy between the two behaviors was the extent to which they could be modified by various doses of chlorpromazine. It is clear from the results (Figures 15 and 16) that avoidance behavior was significantly more susceptible to the effects of small, non-toxic doses of chlorpromazine than was aggressive behavior. A larger dose of chlorpromazine (6.4 mg./Kg.; 1/2 TD_{50}) tended to obscure any differences between aggressive and avoidance behavior. Thus, the results presented in Figure 17 indicate that this dose of drug interfered with the expression of both types of behavior. However, at this dose level slight ataxia was observed in an occasional animal. Consequently, the large decrement in both types of behavior (aggression and avoidance) may have partially resulted from the decreased amount of motor co-ordination produced by this quantity of chlorpromazine.

The above results pertain to the effect of chlorpromazine on frequency of aggressive response to the CS rather than to the quality of aggressive behavior exhibited during such a response. For example, an animal whose response to the CS consisted of 5 seconds of mild aggression received the same score as an animal who responded to the CS by immediately attempting to kill the victim mouse. In view of the above, it was felt that chlorpromazine might alter the quality of the attack pattern and still appear not to interfere with aggressive behavior. Consequently, a scoring system was devised with

which the response to the CS, exhibited by both saline- and chlorpromazine-treated aggressive animals, could be qualitatively rated. With this system, an animal whose attack pattern included components of severe aggression (neck attack; probable kill) received 4 points; one whose attack pattern was characterized by moderate aggression (back and tail biting) received 3 points; one whose attack pattern was limited to mild aggression (sparring and nipping) received 2 points; and non-responders (no aggression) received 1 point. Thus, in a block of 8 trials, an animal which at all times exhibited severe aggression on or before presentation of the CS scored 32 points; whereas an animal which exhibited only mild aggression in the same situation scored 16 points. In this manner, it was possible to contrast the effect of chlorpromazine vs. saline on the quality of aggressive behavior. When this was done (Table 2), it was discovered that doses of chlorpromazine amounting to 1/6 and 1/3 TD_{50} had a negligible effect on the attack pattern exhibited by the experimental animals. Therefore, it must be concluded that small, non-toxic doses of chlorpromazine were ineffective in modifying the quality of aggressive behavior in this species. On the other hand, the large dose of chlorpromazine significantly reduced the quality of response observed in aggressive animals (Table 2), as indicated by the significantly lower mean score. Undoubtedly, this effect may be attributed to the reduced motor co-ordination induced by this quantity of drug.

The observation that sex had comparatively little effect on the aggressive behavior of Onychomys leucogaster deserves a brief comment. Although it is generally agreed

that, in most mammals, males are more aggressive than females (Scott, 1958), comparatively little information pertinent to aggression in females is available. The experimental animal and design employed herein provide a means whereby both the qualitative and quantitative aspects of aggression in male and female mice could be studied.

TABLE 2

THE EFFECT OF CHLORPROMAZINE ON THE QUALITY OF AGGRESSIVE BEHAVIOR EXHIBITED BY ONYCHOMYS LEUCOGASTER

Treatment	Mean Score for 8 Trials
Saline (controls)	26.4
Chlorpromazine (2.1 mg./Kg.; 1/6 TD_{50})	26.2
Chlorpromazine (4.3 mg./Kg.; 1/3 TD_{50})	25.0
Chlorpromazine (6.4 mg./Kg.; 1/2 TD_{50})	18.0*

*significantly different from controls ($P < .025$)

It is manifest from the results discussed above that both aggressive and avoidance behavior can be readily elicited in Onychomys leucogaster by means of a technique which utilizes a conditioning paradigm. However, it is realized that even though a similar experimental technique was employed to establish and study both responses, the two behaviors may not be strictly comparable in all respects. Although apprehension

of shock is thought to be the major motivating factor in the behavior of the avoidance animals, this same factor may be unrelated to the repeated expression of aggressive behavior. This would be especially relevant if a particular combination of external stimuli, i.e., proper environment, CS, and presence of the victim mouse served as a "releaser" (Tinbergen, 1948) which triggered the innate predacious behavior. In this situation, it would be assumed that the tendency for aggressive behavior is continuously present in this animal and that the function of the external stimuli is merely to release or elicit the act. Furthermore, it is also possible that after several successful attacks in which the victim mouse was killed, the reward gained by the expression of aggressive behavior provided sufficient motivation for the continuous repetition of such behavior. A number of more complex experiments would necessarily have to be conducted before any conclusions could be reached relative to the factors motivating aggressive behavior in this species. Nevertheless, the results of these studies indicate that this innate aggressive behavior, once elicited, is more stable than is a learned avoidance behavior in that the former is considerably less susceptible to extinction procedures and the effects of chlorpromazine than is the latter.

VI. GENERAL DISCUSSION

The data presented in these studies demonstrate the feasability of replicating and examining, under appropriate laboratory conditions, the naturally occurring, genetically determined behaviors of several species of mice. Moreover, these data indicate that the hypotheses, tendered at the onset of this investigation (see page 18), relevant to such behaviors may now be accepted. Thus, it was hypothesized that, in an appropriate experimental situation, behaviors predominantly influenced by genetic determinants (innate behaviors) would be more rapidly acquired than those predominantly influenced by environmental determinants (learning and experience). The results of the experiment pertinent to the acquisition of conditioned avoidance responses in Peromyscus maniculatus gracilis (Figure 3) suggest that this assumption is valid. From this study it is evident that a conditioned avoidance response which makes use of a genetically determined behavior (arboreal escape) was more readily acquired than one which depended primarily upon learning (terrestrial escape). For instance, after an equivalent amount of training, animals conditioned to produce an arboreal escape response exhibited 26% more CR's than did those conditioned to produce a terrestrial escape response.

It was also hypothesized that innate behaviors, once established, would be more slowly extinguished than learned behaviors. The results pertaining to the extinction of conditioned avoidance responses in Peromyscus maniculatus gracilis (Figure 4) and to the extinction of conditioned avoidance and aggressive responses in Onychomys leucogaster (Figure 14) support this assumption. The Peromyscus study demonstrated that, after

an equal number of extinction trials, the learned behavior (terrestrial escape response) underwent 31% more extinction than did the innate behavior (arboreal escape response). Even more striking is the difference in the rate of extinction noted in the Onychomys study in which the learned behavior (conditioned avoidance) underwent 64% more extinction than did the innate behavior (aggression) during an equivalent period of time.

Finally, it was hypothesized that innate behaviors not only would be more resistant to the effects of chlorpromazine but also would be less susceptible to alteration by the drug than learned behaviors. A considerable amount of evidence has been presented which tends to support this hypothesis. The resistance of innate behaviors to alteration by chlorpromazine is exemplified by the effect which this drug had on the exploratory behavior of Peromyscus maniculatus bairdi (Figures 10 and 11). In this experiment it was observed that doses of chlorpromazine which markedly reduced this animal's total activity in the maze had little effect on its genetically influenced need to explore the environment systematically. Furthermore, the results of two other chlorpromazine experiments clearly indicate that larger amounts of the drug were necessary to alter genetically determined behaviors than were required to produce a similar effect on environmentally determined behaviors. Hence, it was observed that twice as much chlorpromazine was required to depress significantly an innate avoidance behavior of Peromyscus maniculatus gracilis as was required to produce a similar effect on a learned avoidance behavior in this subspecies (Figures 5 and 6). A similar outcome was observed in the investigation concerning the effect of chlorpromazine on conditioned avoidance and aggressive behavior in Onychomys leucogaster. The results of this

study (Figures 15 and 16) show that small, non-toxic doses of chlorpromazine had a negligible effect on innate (aggressive) behavior, whereas the same amounts of drug markedly interfered with learned (avoidance) behavior. Moreover, significantly more chlorpromazine was required to interfere with the aggressive response in 50% of animals (ED_{50}) than was required to produce a similar effect in animals conditioned to exhibit an avoidance response. Thus, with regard to aggressive and avoidance behavior in Onychomys leucogaster, the ED_{50}'s and 95% confidence limits for chlorpromazine are 5.7 (4.6 - 7.0) and 3.6 (2.4 - 5.4) mg./Kg., respectively.

Why is chlorpromazine less effective in the modification of an innate behavioral response than in a learned response? The fact that innate behavioral responses are more rapidly acquired and/or more slowly extinguished than learned behaviors indicates that the former are more stable. It has been demonstrated with morphine in the cat (Wikler and Masserman, 1943) and with pentobarbital in the pigeon (Dews, 1955) that well-integrated, stable behaviors are more resistant to the actions of drugs than are poorly integrated, unstable behaviors. Therefore, the results obtained with chlorpromazine may be interpreted to reflect the greater stability of innate behaviors and their enhanced resistance to drugs.

In view of the above, it might be expected that innate behaviors should be more resistant than learned behaviors to modification by agents other than chlorpromazine. To test the validity of this assumption, the comparative effect of pentobarbital on innate vs. learned conditioned avoidance behavior in Peromyscus maniculatus gracilis

was determined. The methods employed in this experiment were the same as those used to evaluate the effects of chlorpromazine on the two conditioned avoidance behaviors and have been described in detail previously (see page 26). All trials were executed at the time of peak drug activity (10 minutes) and the following two dose levels employed: 1/2 TD_{50} (7.3 mg./Kg.) and the TD_{50} (14.6 mg./Kg.). From the results of this study (Table 3) it is apparent that, as with chlorpromazine, pentobarbital modifies innate behavior less readily than learned behavior.

TABLE 3

THE EFFECT OF PENTOBARBITAL ON CONDITIONED AVOIDANCE RESPONSES IN PEROMYSCUS MANICULATUS GRACILIS

Dose of Pentobarbital	Per Cent Response (Based on Score)			
	Pan Responders		Pole Responders	
	Saline-treated animals (controls)	Drug-treated animals	Saline-treated animals (controls)	Drug-treated animals
7.3 mg./Kg. (1/2 TD_{50})	86.3	77.6	91.3	92.5
14.6 mg./Kg. (TD_{50})	92.5	73.1*	88.8	90.6

* significantly different from controls ($P < .01$)

For example, at both dose levels, the drug had a negligible effect on the genetically determined means of avoidance (pole response). Since the larger amount of pentobarbital employed produced ataxia in many animals, it is clear that the innate behavior persisted even when the animal's motor co-ordination was slightly impaired. On the other hand, the environmentally determined means of avoidance (pan response) was considerably more susceptible to the effects of the drug in that the smaller dose of pentobarbital tended to depress the response and the larger dose markedly depressed it ($P < .01$).

When a comparison is made between the effect of chlorpromazine on these avoidan behaviors (Figures 5 and 6) and the results illustrated in Table 3, it is evident that chlorpromazine contrasts sharply with pentobarbital. Chlorpromazine effectively interferes with both learned and innate avoidance responses in non-toxic doses of 1/8 and 1/4 TD_{50}, respectively. In order to obtain similar effects with pentobarbital, doses of the drug equivalent to the TD_{50} are required to interfere with the learned avoidance response and doses larger than the TD_{50} are required to interfere with the innate avoidance response. Thus, it is obvious that chlorpromazine is considerably more selective in its behavioral effects than is pentobarbital.

From this entire investigation, three major facts pertinent to innate behaviors emerge: (1) such behaviors are more readily evoked than learned behaviors, (2) they are more slowly extinguished, and (3) they are more resistant to alteration by centrally acting drugs. Moreover, it would appear that drugs with sedative-hypnotic properties, such as pentobarbital, can be distinguished from drugs with more selective

central nervous system depressant properties by means of laboratory techniques which utilize these behaviors. In view of the above, a thorough examination of the innate responses of a variety of other animal species might be worthwhile. Finally, since the present investigation was limited to an examination of the effects of a single ataractic and sedative-hypnotic drug on innate behavior, it should be extended to include a variety of centrally acting drugs. Such a study might not only contribute further to an understanding of behavioral processes but might also reveal innate responses which could be employed in screening procedures applicable to the search for new psychotropic agents.

VII. SUMMARY AND CONCLUSIONS

The experiments presented in this investigation were conducted to permit an examination under controlled laboratory conditions of some genetically determined (innate) behaviors of several species of mice. In most instances, such behaviors were compared with other responses which, in the same animals, were considered to be predominantly influenced by environmental (learned) determinants. The comparison was made on the basis of rate of response acquisition, rate of response extinction, and/or susceptibility of the response to the effects of chlorpromazine. In the drug studies, all behavioral trials were conducted at the time of peak drug activity (based on neurotoxicity), and the dose levels employed represented fractions of the TD_{50}.

A. The Effect of Chlorpromazine on Two Types of Avoidance Behavior

A series of experiments were designed to compare the conditioned avoidance behavior of a semi-arboreal mouse (Peromyscus maniculatus gracilis) in a situation which demanded an innate (arboreal; pole climbing) response with its avoidance behavior in a situation which demanded a learned (terrestrial; pan sitting) response. The data obtained indicate that the avoidance behavior based on the innate response was more readily acquired, less readily extinguished, and less susceptible to the effects of small, non-toxic doses of chlorpromazine than was the avoidance behavior based on the learned response.

B. The Effect of Chlorpromazine on Exploratory Drive

A complex electronic maze was utilized to evaluate the investigative behavior of

two closely related subspecies of deermouse; Peromyscus maniculatus gracilis and Peromyscus maniculatus bairdi. The maze was specifically designed to resemble more closely an environment which occurs in the natural habitat of bairdi than in that of gracilis. Three measures of exploratory activity were employed: latency to enter the maze, total maze activity, and blind alley maze activity. An examination of the results pertinent to the exploratory behavior of the two subspecies during a one-hour period in the maze revealed that all animals exhibited similar latencies and that all animals (with the exception of gracilis males) exhibited a similar amount of total maze activity. However, it was evident that bairdi demonstrated a greater inclination to explore all blind alleys and, hence, possessed a more systematic pattern of exploratory behavior than did gracilis. These results suggest that, in bairdi, the maze exploratory activity may have been motivated by a genetically determined need to explore blind alleys thoroughly, whereas, in gracilis, the novelty of the environmental situation may have provided the motivation for exploration.

The administration of small, non-toxic doses of chlorpromazine had little effect on the quantity or quality of exploratory behavior exhibited by gracilis. On the other hand, equivalent doses of the drug significantly increased the latency of bairdi to enter the maze and significantly decreased the amount of total maze activity exhibited by this subspecies. However, the drug had little effect on this animal's systematic exploration of the maze. A pilot study excluded the possibility that the variance in the maze results observed between the two chlorpromazine-treated subspecies was related

to a selective effect of the drug on the amount of horizontal or vertical spontaneous motor activity. These results suggest that small, non-toxic doses of chlorpromazine do not interfere with exploratory activity when such behavior is motivated either by a large amount of novelty, as with gracilis, or by genetic determinants, as with bairdi. All observations in this study were characterized by a considerable amount of intra-subspecies variability.

C. The Effect of Chlorpromazine on Aggressive and Avoidance Behavior

The innate, aggressive behavior of a small, predacious mouse (Onychomys leucogaster) was compared with a conditioned avoidance behavior elicited in this same specie In both behavioral situations the animals were trained to forestall a noxious stimulus by performing an appropriate motor response. For avoidance behavior, this response consisted of finding and remaining on a "safe area" pan for a period of 5 seconds, where as the appropriate aggressive response consisted of a continuous attack on a victim mouse for a similar period of time. Although there was no difference in the rate of acquisition of the two responses, the aggressive behavior was considerably more stable than the avoidance behavior in that the former was significantly more resistant to extinction than was the latter. Further evidence for the greater stability of the aggressive behavior is provided by the fact that significantly larger quantities of chlorpromazine were required to decrease the frequency of expression of this response than were necessary to produce a similar effect on avoidance behavior. Moreover, an evaluation of the effect of chlorpromazine on the quality of aggression evoked in Onychomys

leucogaster by means of this procedure indicates that this response was depressed only after a dose of the drug which reduced the animal's motor co-ordination. It was also observed that, in contrast with most mammals, sex had comparatively little effect on the aggressive behavior of this species.

D. Conclusions

From the results presented, it can be concluded that innate behavioral patterns may be replicated in the laboratory if the experimental apparatus and procedures are specifically designed to provide stimulus conditions and response opportunities favorable to the expression of such behaviors. Moreover, such behaviors are more readily evoked, less readily extinguished, and less susceptible to alteration by centrally acting drugs than are behaviors whose expressions are predominantly dependent upon non-genetic (learned) determinants. Also, the results suggest that drugs which selectively depress the central nervous system, e.g., chlorpromazine, may be delineated from drugs which are less selective, e.g., pentobarbital, by means of techniques which utilize innate behaviors. Thus, such behaviors, because of their marked stability, may be especially valuable in procedures designed to evaluate new psychotropic agents.

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THE EFFECTS OF CHLORPROMAZINE UPON SOME INNATE BEHAVIORS OF MICE

by

Harold H. Wolf

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Ewart A. Swinyard — Chairman, Supervisory Committee

Department of Pharmacology
College of Pharmacy

University of Utah
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Some innate (genetically determined) behaviors of several species of mice were examined and compared, in most instances, with learned (environmentally determined) behaviors of these same animals. The comparison was made on the basis of rate of response acquisition, rate of response extinction, and/or susceptibility of the response to the effects of chlorpromazine.

The conditioned avoidance behavior of a semi-arboreal mouse (Peromyscus maniculatus gracilis) was examined in a situation which required an innate (arboreal; pole climbing) means of avoidance as compared with a situation which required a learned (terrestrial; pan sitting) means of avoidance. It was observed that conditioned avoidance behavior based on an innate response was more readily acquired, less readily extinguished, and less susceptible to the effects of small, non-toxic doses of chlorpromazine than was conditioned avoidance behavior based on a learned response.

The exploratory behavior of two closely related subspecies of deermouse (Peromyscus maniculatus gracilis and Peromyscus maniculatus bairdi) was evaluated by means of a complex electronic maze which was designed to resemble more closely an environment occurring in the natural habitat of bairdi than in that of gracilis. Three measures of exploratory activity were employed: latency to enter the maze, total maze activity, and blind alley maze activity. With the exception of gracilis males, all animals exhibited similar latencies and similar amounts of one-hour total maze activity. However, bairdi demonstrated a more systematic pattern of maze activity than did gracilis in that the former had a greater inclination to explore all blind alleys. These results suggest that

in gracilis the novelty of the environment may have provided the motivation for exploration, whereas in bairdi this activity was probably motivated by a genetically determined need to explore blind alleys thoroughly.

The administration of small, non-toxic doses of chlorpromazine had little effect on either the quantity or quality of exploratory behavior exhibited by gracilis or on the systematic pattern of maze exploration exhibited by bairdi. These results suggest that small, non-toxic doses of the drug do not interfere with exploratory activity when such behavior is strongly motivated by novelty, as in the case of gracilis, or by genetic determinants, as in the case of bairdi.

The innate aggressive behavior of a small, predacious mouse (Onychomys leucogaste was compared with this animal's avoidance behavior. A similar conditioning paradigm was used in both studies. It was observed that although there was no difference in the rate of acquisition of the two responses, the aggressive behavior was considerably more resistant to extinction than was the avoidance behavior. Moreover, significantly larger quantities of chlorpromazine were required to depress aggressive behavior.

The data obtained in this investigation indicate that innate behavioral patterns may be replicated in the laboratory if the experimental apparatus and procedures are specifically designed to provide stimulus conditions and response opportunities favorable to the expression of such behaviors. Moreover, such behaviors are more readily evoked, less readily extinguished, and less susceptible to alteration by centrally acting drugs than are behaviors whose expressions are predominantly dependent upon non-genetic

(learned) determinants. Also, the results suggest that drugs which selectively depress the central nervous system, e.g., chlorpromazine, may be delineated from drugs which are less selective, e.g., pentobarbital, by means of techniques which utilize innate behaviors. Thus, such behaviors, because of their marked stability, may be especially valuable in procedures designed to evaluate new psychotropic agents.